

ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

Hearing held 8th floor 180 Dundas Street West Toronto, Ontario

Commissioner

P.S.A. Lamek, Q.C.

The Honourable Mr. Justice S.G.M. Grange

Counsel

E.A. Cronk

Associate Counsel

Thomas Millar

Administrator

Transcript of evidence for November 29, 1983

VOLUME 71

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1	ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN		
2	AND RELATED MATTERS.		
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4	Hearing held	on the 8th Floor,	
5	180 Dundas Street West, Toronto, Ontario, on Tuesday, the 29th		
6.	day of November, 1983.		
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8	THE HONOURABLE MR. JUSTIC	E S.G.M. GRANGE - Commissioner	
9	THOMAS MILLAR	- Administrator	
10	MURRAY R. ELLIOT	- Registrar	
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12		Dement for Excle Person use	
13	APPEARANCES:		
14	E. CRONK	Commission Counsel	
15	D. HUNT ) L. CECCHETTO)	Counsel for the Attorney General and Solicitor General	
16	II. CICCIIII 107	of Ontario (Crown Attorneys and Coroner's Office)	
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23		Nurses' Association of Ontario and 35 Registered Nurses at The Hospital for Sick Children	
24		the majorest tot been different	

(Cont'd)

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1	APPEARANCES: (	Continued)
3	D. BROWN	Counsel for Susan Nelles - Nurse
4	G.R. STRATHY) E. FORSTER )	Counsel for Phyllis Trayner - Nurse
5	J.A. OLAH	Counsel for Janet Brownless - R.N.A.
6	B. JACKMAN	Counsel for Mrs. M. Christie - R.N.A.
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9		child Stephanie Lombardo); and Heather Dawson (mother of deceased child Amber Dawson)
10	W.W. TOBIAS	Counel for Mr. & Mrs. Hines (parents of deceased child Jordan Hines)
12	J. SHINEHOFT	Counsel for Lorie Pacsai and Kevin Garnet (parents of deceased child Kevin Pacsai)
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INDEX OF WITNESSES NAME Page No. KAUFFMAN, (Dr.) Ralph; Resumed Direct Examination by Ms. Cronk (Cont'd) 5543 INDEX OF EXHIBITS No. Description Page No. Excerpt from Volume on Pediatric Pharmacology, Digoxin Pharmacokinetics in Premature Infants. Expurgated Minutes of Meeting of August 27, 1982. Expurgated copy of Atlanta Report. 





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--- Upon commencing at 10:00 a.m.

multiplier effect.

DR. RALPH KAUFFMAN, Resumed

THE COMMISSIONER: Yes, Miss Cronk.

MS. CRONK: Good morning, sir.

DIRECT EXAMINATION BY MS. CRONK: (Continued)

Q. Good morning, Doctor.

A. Good morning.

MS. CRONK: Mr. Commissioner, you will recall yesterday during the course of Dr. Kauffman's evidence he made reference to a recent article by Dr. Hastreiter, it had to do with the

Q. Dr. Kauffman, is this the article to which you were referring?

A. Yes, I believe it is.

MS. CRONK: Thank you. Sir, the article was published in 1982 in the Volume on Pediatric Pharmcology, can that be the next exhibit please?

THE COMMISSIONER: Yes, Exhibit 268.

--EXHIBIT NO. 268: Excerpt from Volume on Pediatric Pharmacology, Digoxin Pharmacokinetics in Premature Infants.

MS. CRONK: Thank you, sir.

THE COMMISSIONER: Yes.

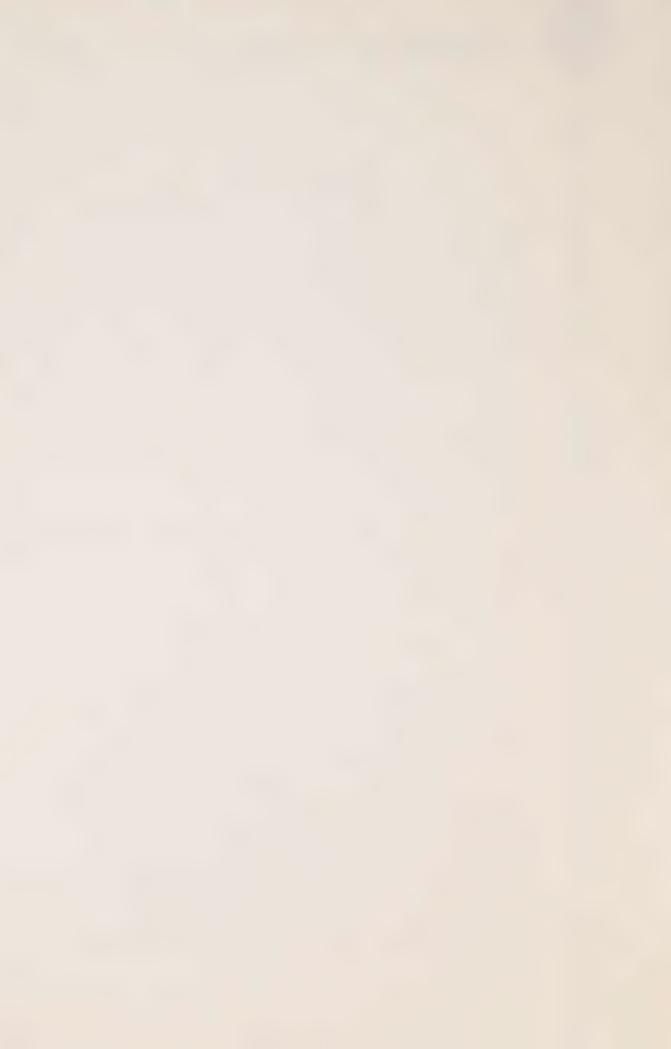
MS. CRONK: O. Dr. Kauffman, yesterday at the end of the day you had outlined for us the various calculations that you had made in the case of Justin Cook, to estimate a maximum amount of digoxin that might have been administered to the child and which would account for the levels of digoxin found both in the serum and in his tissues. You outlined for us the various assumptions which you felt you were required to make in arriving at that estimate.

Your first assumption as I understood it was that 100 per cent of the dose had been infused, do I have that correctly?

A. That is correct.

Q. Does that assumption, Doctor, necessarily flow from the fact that you were estimating a maximum amount, and if it does not can you help me as to why you made that assumption?

A. It flows in part because I was estimating a maximum amount; and it also flows from the assumption that when you give a drug intravenously 100 per cent of it gets in. In practicality that may not always true depending on the mechanism which is used for infusing the



And Doctor, as I understand

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it the second assumption that you made in arriving at that estimate was that death had occurred more

drug, but that assumption is usually made.

correctly?

A. That is correct.

than five hours after the dose; do I have that

Q. And in that context, Doctor, were you referring to death per se, or as you mentioned yesterday, were you referring to the time of sampling for the ante mortem samples?

A. I actually intended to say that the timing was back from the time that the sample was obtained, because we have to measure from the time the sample was obtained, we don't have any information obviously beyond the time the sample was drawn.

Q. Doctor, can you help me please as to why you made that assumption?

A. What, the greater than five

Q. Yes.

A. Because to estimate a maximum dose that might be required one has to assume the largest volume of distribution, or the



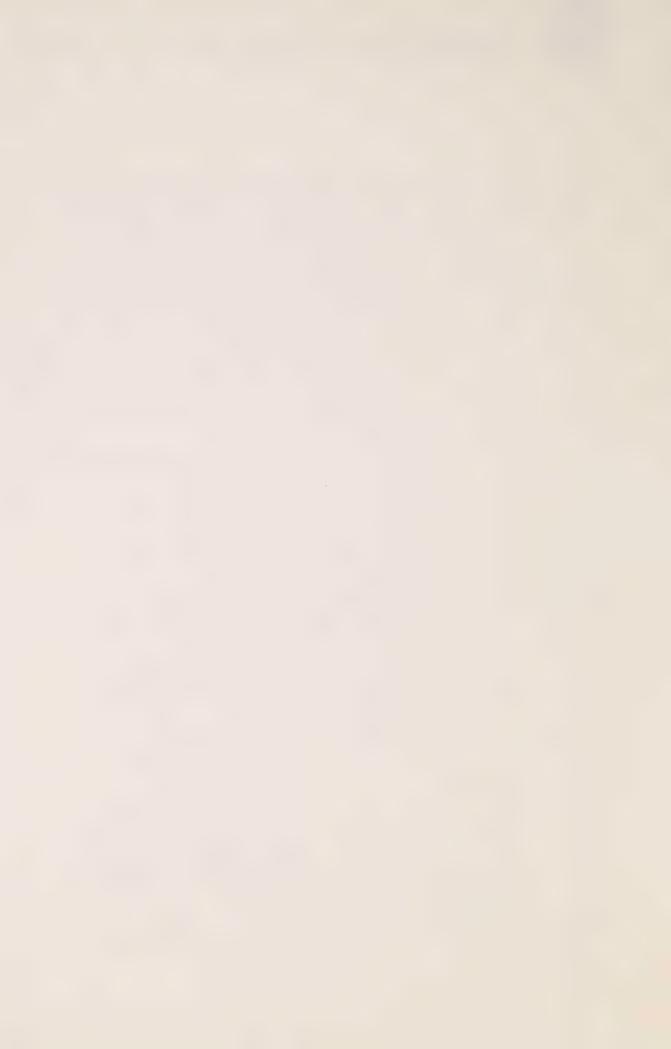
so-called beta distribution, or the time after which distribution into the tissues has been completed. Estimating that the half life of distribution is somewhere between 30 minutes and 60 minutes and it takes five half lives to be certain that that has taken place, I assumed a period of greater than five hours. Since I can't put a non-specific number into the equation I picked a specific number and that was six hours.

Q. Well, Doctor, you will recall that yesterday I drew to your attention that Dr. Spielberg had testified that in his view the time for the distribution phase during the alpha phase was between two and a half and four hours.

As I recall it you told me that in broad terms you agreed with that approximation in the distribution phase although it potentially could be longer; do I have that correctly?

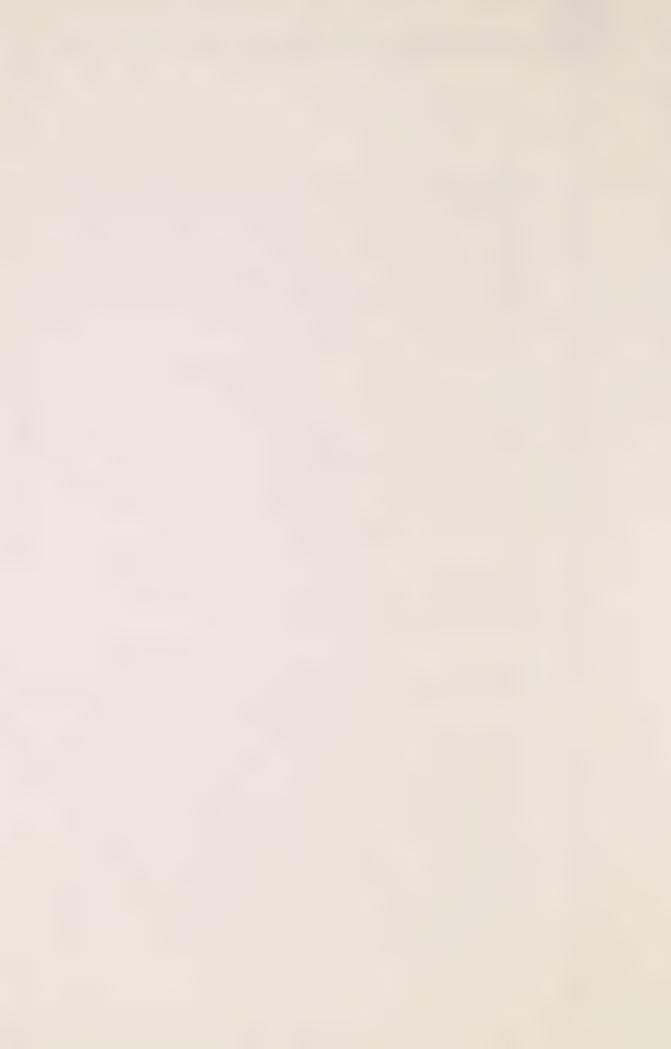
A. You mean for it to be complete?

- Q. For it to be complete.
- A. Yes, I would in general agree with that, I suppose it could be longer in individual cases.
  - Q. So in this case then,



Doctor, in making the assumption that the time of sampling of that ante mortem sample taken during resuscitation efforts was greater than five hours from the time of the dose, you were therefore assuming that complete distribution had taken place with respect to the drug?

- A. That is correct.
- Q. And Doctor, the next assumption that you made, if I understood you correctly yesterday, was that a distribution equilibrium with the peripheral compartment was complete at the time of death; did I understand that correctly?
- A. That equilibrium, that an equilibrium existed between the central and the peripheral compartment, yes.
- Q. Can you help us, Doctor, please as to what you meant by using that assumption?
- A. That essentially is just another way of saying distribution has been completed once the amount of digoxin in the body has distributed to the extent it is going to distribute, an equilibrium situation exists between the amount of drug in the various tissues and that in the serum or the plasma compartment. That is not to say that the concentration is the same, obviously it is not,



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but there is some ratio that exists between that equilibrium which is assumed to generally maintain it until another dose is administered.

Q. So that the stage, Doctor, where there is a constant ratio between the amount of digoxin in the tissues and the amount of digoxin in the serum?

A. That is correct, that assumption is made when one says the distribution is complete, you assume that there then is a constant ratio maintained between the several compartments.

Q. Doctor, once again in making that assumption and recording it in your report you spoke of the time of death. Again were you talking about the time of death per se, or the time of sampling for that ante mortem sample?

A. I think I have to define that as the time of sampling for the purposes of the calculations, because the time of death to me was ill-defined because it was taking place over a period of many minutes.

 $\Omega$ . I understand, Doctor. Since discussing the matter yesterday, Doctor, I checked our exhibits and I can now tell you that the sample



taken during the resuscitation effort, which resulted in a level of 72 nanograms, was taken at 4:30 a.m., that is 10 minutes after the Code 25 was called. Do I have correctly then that you assuming that by 4:30 a.m. this state of equilibrium, or the constant ratio between the amount of digoxin in tissue and serum had been achieved?

A. In calculating the maximum possible dose?

Q. Yes.

A. The assumption was made, yes.

Q. Thank you, Doctor. Doctor,

your fourth assumption as I understood it was that the elimination half life of digoxin in this instance was some 30 hours?

A. That is correct.

Q. Doctor, were you referring in that context by virtue of the elimination feature to the beta phase?

A. That is correct.

Q. We have heard in evidence,
Dr. Kauffman, from Dr. Spielberg, that in his
estimation the half life which applies for digoxin
during the beta phase is approximately 20 to 80 hours
Can you help me as to why in this instance you



selected 30 hours?

reviewed I think reported values for the beta half life would have been anywhere from 15 to 80 some hours, which includes the rate that you just quoted me. The 30 to 35 hours, 36 hours, somewhere in the 30's is a mid-point in that range and somewhat of an average, so I picked, without having any reason to pick either extreme, I picked the middle point for the purposes of the calculation.

Q. And does the half life in the elimination phase, Doctor, has anything to do with the body weight of the particular patient and the clinical condition of the patient?

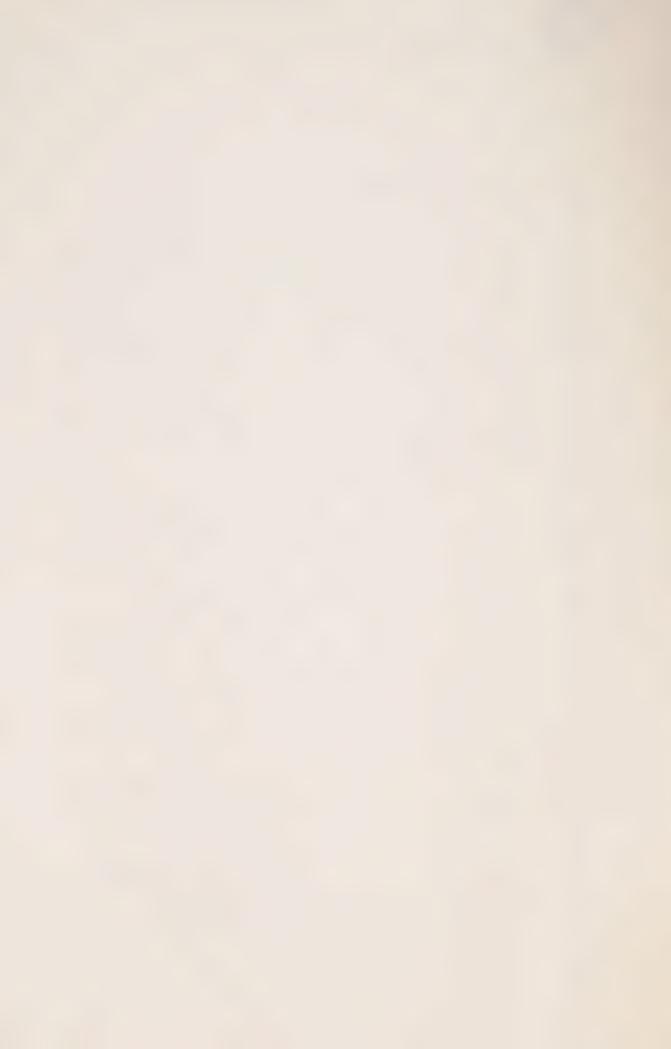
A. Well half life doesn't have anything to do with the body weight. It may have to do with the physiological maturity of the individual and it may have to do with the clinical condition of the individual.

Q. It is in some sense then related to the age of the patient, Doctor?

A. Yes.

Q. And the older the patient presumably the lengthier the time of elimination?

A. No.



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Q. It is shorter?

A. In the period from infancy, from newborns who during the first year of life the newborn tends to have slower elimination temporarily, and then as they mature during the first year their elimination processes tend to become in fact more rapid.

Q. Doctor, the fifth assumption as I understand it was much related to one that you have made earlier, and that was that the time of death was six hours following the injection. Once again are we talking time of death or the time of sampling?

A. We are talking time of sampling for the purposes of this calculation.

Q. And why, Doctor, in this case did you select six hours as opposed to anything else greater than five?

A. Simply because that was the shortest time, the shortest time beyond within reasonable time of the five hour limit that I have arbitrarily set for distribution to take place.

One could pick I suppose a longer time up to 12 hours, the calculation really wouldn't change very much. If one choose 6, 8 or 12 hours it really



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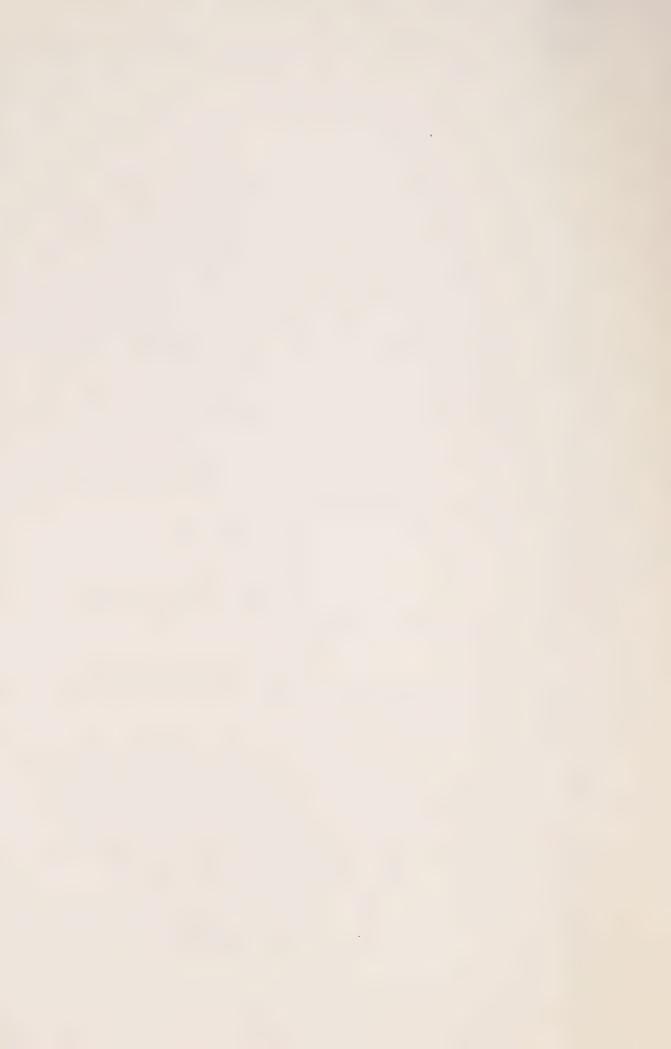
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wouldn't change the calculation very much. Q. Well, Doctor, on the basis of the time that you did select, and that six hours following the injection and having regard to the fact that the sample was taken at 4:30 in the morning, that will place the time of the injection, Doctor, if measured back from the sampling time to approximately 10:30 p.m. on the evening of March 21st would it not? Α. If you did your arithmetic correct that is right. 4:30 back six. Q. Α. I think so. 0. In fact, Doctor, do you consider that likely? Α. maximum calculation.

No, I don't consider that likely, that was an outside number used for the

Doctor, your sixth assumption had to do with the weight of the child and we have seen that you assumed 5.37 kilograms. Your seventh assumption had to do with the volume of distribution and you assumed 10 litres per kilogram?

- That is correct. Α.
- Once again, Doctor, are Q.



we talking about the alpha or the beta phase for that assumption?

A. The beta phase.





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O. Dr. Spielberg in his evidence
I can tell you, Dr. Kauffman, in estimating his
maximum dose calculation used a volume of distribution
of some 15 hours.

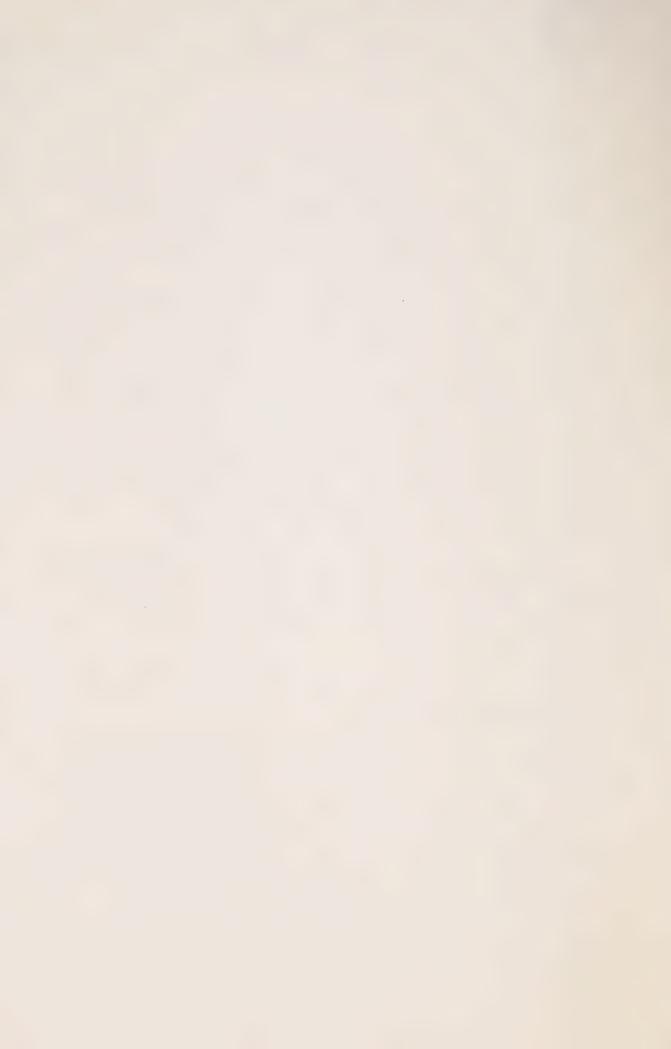
Can you help us as to why in this case you selected 10 hours -- I'm sorry, 10 litres?

A. Well, again, that is a midrange number from a wide range. The numbers I have
seen vary from approximately 6 litres per kilogram to
15 litres per kilogram and I have no reason to pick
either extreme so I picked a mid range when I used
the reported values in the literature.

Q. Doctor, your eighth and last assumption in this calculation as I understand it was that there was an elimination rate constant of .0231 hours.

Can you help us as to what that assumption entails?

expressing the half life. That is that the elimination rate constant represents the fraction of the drug remaining in the body which is excreted during every unit of time. You can express it in terms of minutes, hours, days or whatever unit of time you want. So it is a fraction of the drug that is eliminated during



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24 25 that period of time.

In this case we are talking about a half life of hours, so the elimination rate is a fraction of the drug that is eliminated every hour of that which remains --

- In the body of the child. 0.
- -- in the body of the child.
- All right. Doctor, on the 0. basis of these various assumptions you have told us that the maximum dose which you calculated was approximately 4.3 mg. Do I have that correctly?
  - Α. That is correct.
- You have also told us, doctor, that related to intravenous administration.
- Α. That was part of the assumption, that is correct.
- Doctor, you have also told us 0. that leaving aside the possibility of intravenous administration as the route by which the drug was administered, you attempted to estimate the amount of oral elixir which could produce the serum and tissue concentrations found in this child.
  - Α. That is correct.
  - Do I have that correctly? 0.
  - A. Yes.



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Ω. Can you tell us, doctor, what the amount or amounts were that you estimated in this regard, assuming an oral route of administration?

A. If one assumes that the infant died within an hour after getting an oral dose, a dose of approximately 0.7 mg. can theoretically provide such a level, and this would be a volume of the pediatric elixir of approximately 14 millilitres.

O. And assuming, doctor, that the child died sometime after one hour from the time of administration, what is your calculation in that regard?

A. Well, again I used the same time assumptions that I used for the intravenous dose which was six hours.

If you estimate that the child died six hours after the oral dose, a dose of approximately and I am assuming with the oral estimates that 70% of the dose is absorbed from the gastrointestinal tract.

Q. Yes.

A. If I assume death six hours after -- I mean the sample was obtained six hours after the dose, a dose of approximately 6 mg. would be required, and this would be contained in a volume of the pediatric elixir of approximately 120 millilitres.



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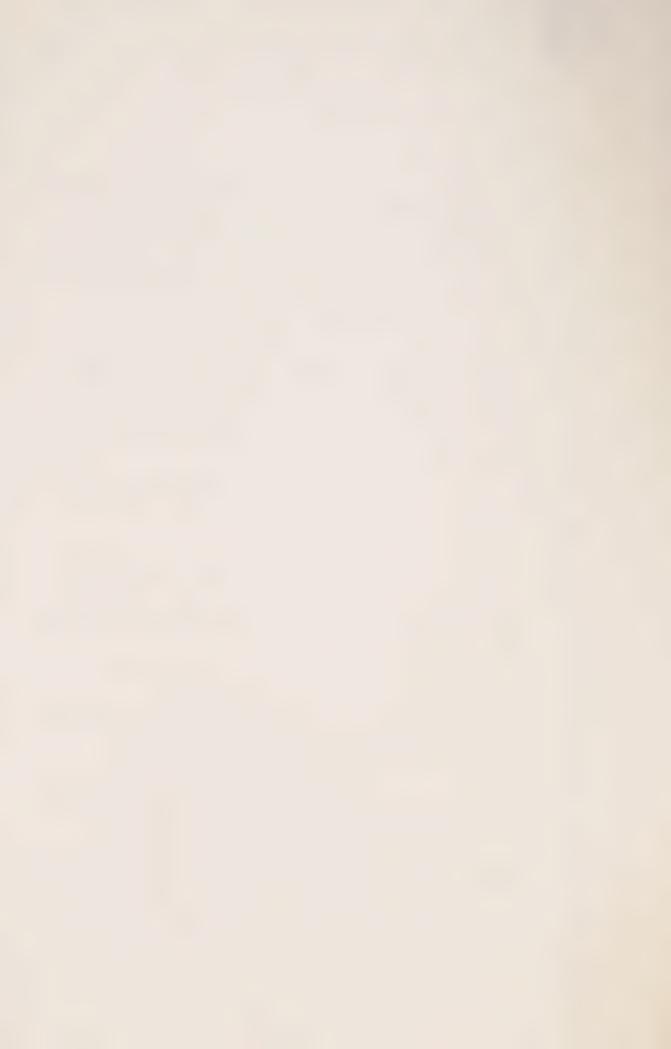
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Well, doctor, can we deal 0. first with the first scenario, and that is the hypothesis that death occurred within an hour. How much digoxin elixir are we talking about having regard to your estimated volume?

Α. In terms of volume it is 14 millilitres as I said. That would be approxmately one half ounce and I think the elixir bottles, if I am not mistaken, come in 100 millilitre bottles. Is that correct?

- That is the evidence, Dr. 0.
  - Okay. Α.
- So on the first scenario we 0. are talking approximately one half ounce of the oral elixir?
  - Α. That is correct.
- Do you consider administration 0. by that route and that amount likely, doctor?

Α. I think it is possible looking at the condition that this child was in at the time this might have taken place shortly before the sample was drawn. I think it is unlikely that it would have been feasible or easy to get that much volume into the child and have the child swallow it.



**B5** 

Q. Assuming, doctor, that it
was possible to administer that amount of volume and
that the child did in fact ingest it or swallow it,
could that amount of oral digoxin elixir account for
the concentrations of digoxin found in the tissues
of this child assuming as you did that the child died
within one hour of the drug having been administered?

A. Or the sample was obtained within one hour.

- Q. I'm sorry, that is right.
- A. I think it is -- well, no,
  I don't think it is possible because by definition

we calculate that dose -- I have assumed that no distribution took place. That is one of my assumptions with the minimum dose, that no distribution in the tissues out of the central compartment has as yet taken place, and that is inconsistent with the tissue level, certainly a tissue level of 1100: and some nanograms per gram.

Q. Well, indeed, doctor, having regard to the concentrations found in the tissues we know, do we not, that some distribution must have taken place?

A. Yes. Yes, I think it did. It obviously had to.



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	Ω.	And,	doctor,	dealing	with	your
second scenario,	and th	hat is	that t	he time	of	
sampling occurred	l six l	hours	after i	ngestion	, you	have
told us that that	would	d be i	n your	view a d	ose of	990 140
some 6 mg. with a	a volum	me of	100 mil	lilitres	•	

I take it, doctor, that as the oral elixir came in a form with a volume of 100 millilitres, you are talking in that instance of more than one full bottle of oral elixir?

- Yes, that is correct.
- Ω. Right. And, doctor, do you consider administration by that route, given that amount, likely?
- No, I think that is highly Α. unlikely.
- And perhaps stating the 0. obvious, doctor, is that simply because of the amount of the drug that would be required?
- I think because of the quantity, to get the baby to drink a full nipple bottle full of digoxin elixir is probably --
  - 0. Next to impossible?
  - Next to impossible, yes. Α.
- I take it then, doctor, under Q. either scenario, be it the sampling time within



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one hour or the second scenario sampling time six hours after administration, you consider both of those alternatives unlikely, and therefore feel that oral administration is unlikely?

A. For those reasons and there was another reason I believe that was the second autopsy, intestinal contents, digoxin in the intestinal contents was measured and it was a very small amount.

Had the child recieved this kind of dose orally within a few hours prior to death I would have expected many thousandfold higher concentrations in the gut.

- Q. Well, doctor --
- A. So that along with the lack of probability that a baby could be in this baby's condition could be administered this volume orally, I discount the probability of oral administration.
- Ω. Is that true, doctor, even if the minimum amount as opposed to the maximum had been administered and that is that half ounce of the oral elixir?
  - A. Yes.
- Q. You would still expect a higher level in the gut?
  - A. Oh, yes, because the oral elixir,



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doctor --

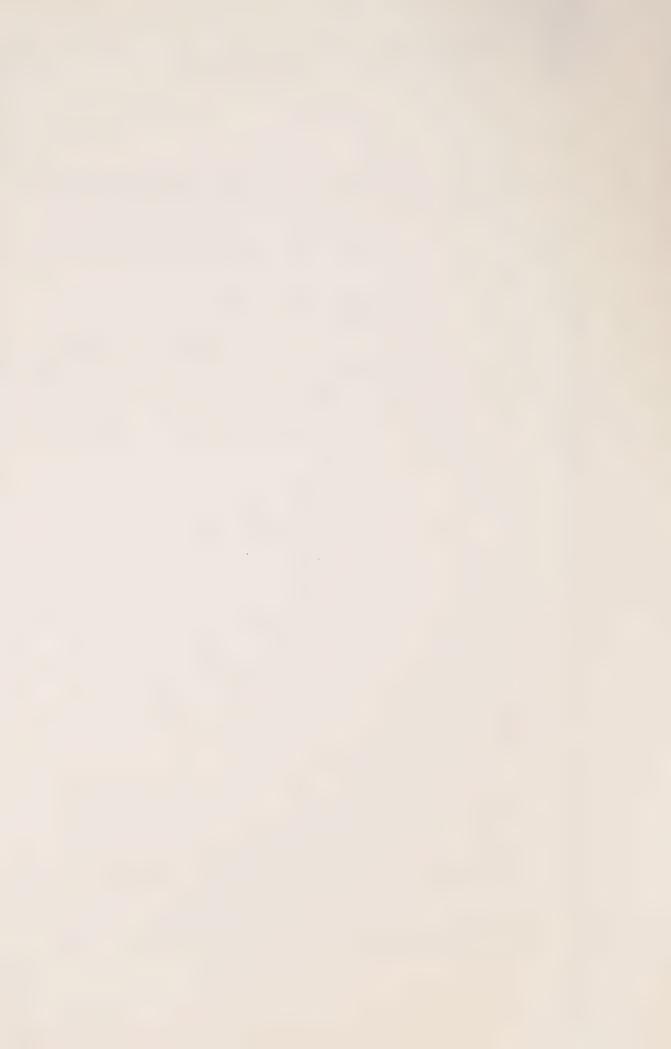
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the amount in the gut I think was in the neighbourhood of 600 nanograms.

- $\Omega$ . Well, would it help you,
- A. Something like that.
- Ω. From Mr. Cimbura's reports a sample of the gastric contents were sampled, and that resulted in 34 nanograms of digoxin, and a sample of the small bowel and contents resulted in a level of 621 nanograms.
- A. Well let me illustrate why I say I don't think the baby could have received digoxin orally then: That is there is 50,000 nanograms in each millilitre of that elixir. So if you multiply 50,000 times 14 millilitres you will get the number of nanograms that the baby would have received orally. It is a hundred thousand times what was found in the gut so it is totally implausible to me that that could have occurred.
- Q. May we turn then, doctor, to the route of administration and the amount of the dose or the volume of the dose that you consider most likely to have occurred in this situation.

You have said at page 5 of your first reporting letter to Mr. Wiley, doctor, in the



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first full paragraph on the page, that the dose administered was probably somewhere between the extreme estimates that you made. That was your conclusion regarding the amount of the dose?

- A. That is correct.
- Q. Am I correct in concluding, therefore, doctor, on the basis of what you told us about your estimates that you feel the likely dose to have been something greater than .5 mg. and something less than 4.3 mg.?
  - A. Yes, that is correct.
- $\Omega$ . Why, doctor, do you feel that the minimum dose is unlikely?



C BB/cr 

	Α.	Well, as	I said a mo	oment ago,
the minimum	dose was	calculated	based on th	ne
assumption t	hat no di	stribution	out of the	central
compartment	had occur	red at the	time the sa	ample was
obtained and	that is	totally in	consistent w	with a
tissue level	in the h	eart of ll	00 nanograms	per gram.
So, that cal	culation	cannot be	consistent w	with the
tissue level	in fresh	tissue th	at was measu	ired.

On the other hand, the maximum concentration in my mind is unlikely because I think it is difficult to conceive of the child surviving for that length of time with that much digoxin on board. I think that it would be highly unlikely for the child to survive with no symptoms for a six hour period with that large a dose.

Q. Thank you, Doctor. Doctor, you also told us yesterday, as I understood your evidence, with respect to the minimum dose calculation that translated into number of vials that would result in approximately 10 vials of the paediatric ampules and one adult vial. Do I have that correctly?

A. That is correct.

THE COMMISSIONER: I am sorry, what is this for? Oh, that's right, yes, that's right.

MS. CRONK: This is for the minimum



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dose, sir.

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MS. CRONK: Q. That being the case, Doctor, given that your opinion is that the minimum dose is an unlikely amount that could have been administered to this child, are you also then telling us that in your view it is unlikely that one adult ampule of digoxin could have achieved these levels in this child?

THE COMMISSIONER: Yes.

Well, based on my estimates I think, yes, it is unlikely. I think it had to be more, something more than that; how much more it is difficult to say.

All right. Doctor, may we turn now then to the question of timing and what your best judgment is given your minimum and maximum extremes as to the likely time the dose was administered. As I recall your evidence yesterday, you said that in your view the dose was administered somewhere between one to three hours prior to the taking of the resuscitation effort blood sample. Do I have that correctly?

- I believe that is correct.
- All right. And in the face, Doctor, of the fact or the information now that that

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sample was taken at 4:30 in the morning, and I should say, sir, that that is reflected in the requisition form that was completed on the ward, which is part of Exhibit 32A at Tab 36. In recognition, Doctor, that the sample was taken at 4:30 in the morning, does that then place the most likely time of administration in your view some time between 1:30 and 3:30 a.m. on March 21st?

A. In those terms, yes, it would.

Q. Doctor, may we turn to the likely method of administration in your best judgment. You have said again, referring to page 5 of your report to Mr. Wiley, that you consider it - to help you, Doctor, I am sorry, I am referring to the latter half of the first full paragraph of your report. You have said that:

"It is most likely that the dose was injected somewhere in the lower intravenous line and allowed to infuse with the intravenous fluid."

Do you see that, Doctor?

- A. Yes, I am looking at that.
- Q. May I ask you, Doctor, what the basis is for your opinion in that regard?



A. Well, as I said, I ruled out oral administration for the reasons I have described. The other reasonable methods of administration would include intramuscular injection, which I discounted because I was told that the autopsy indicated no injection sites and it was inconceivable to me that that large a volume could be injected without being apparent at autopsy. So, I was left with intravenous administration which was quite plausible anyway because an intravenous line was running at the time the baby arrested.

Considering intravenous administration

I could then consider whether it might have been placed in the bag of fluid, intravenous fluid, whether it might have been placed in the volume chamber below the bag or whether it could have been placed somewhere in the line between the volume chamber and the patient or directly into a separate intravenous site or at the site of the needle that was already being used for the intravenous infusion.

It seemed quite implausible to me that it would be, the dose would be placed in the bag of intravenous fluid or the volume chamber because if that were the case it would take a prolonged period of time with the usual intravenous flow rates for



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the dose to infuse into the patient. We know from studies with other drugs that with the flow rates that are commonly used in infants this size, it may take anywhere from 2 to 6 hours to infuse 90 per cent of the dose of the drug when it is placed in the bag or in the volume chamber.

So, I didn't think that was a likely possibility.

The other thing that led me to discount that was that one of the samples that Mr. Cimbura assayed for digoxin was I think fluid obtained from the bag of intravenous fluid and his assay showed that there was no digoxin present. So, that confirmed my assumption that there was no digoxin in the bag of intravenous fluid.

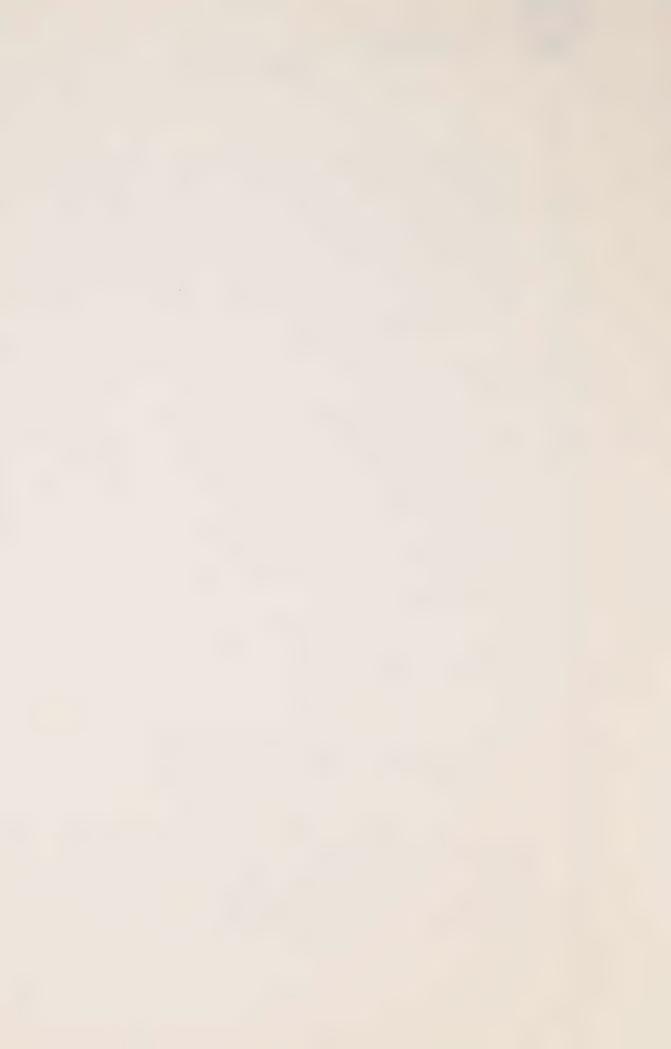
Well, could I just stop you Q. there for a moment, Doctor.

> Α. Yes.

Could I ask you, do you still Q. have a copy of Mr. Cimbura's report there?

> Α. I think I do.

Could you turn please to his first report dated January 11, 1982 at page 3. The only two samples, Doctor, of which I am aware with respect to the IV fluid or related to the IV fluid



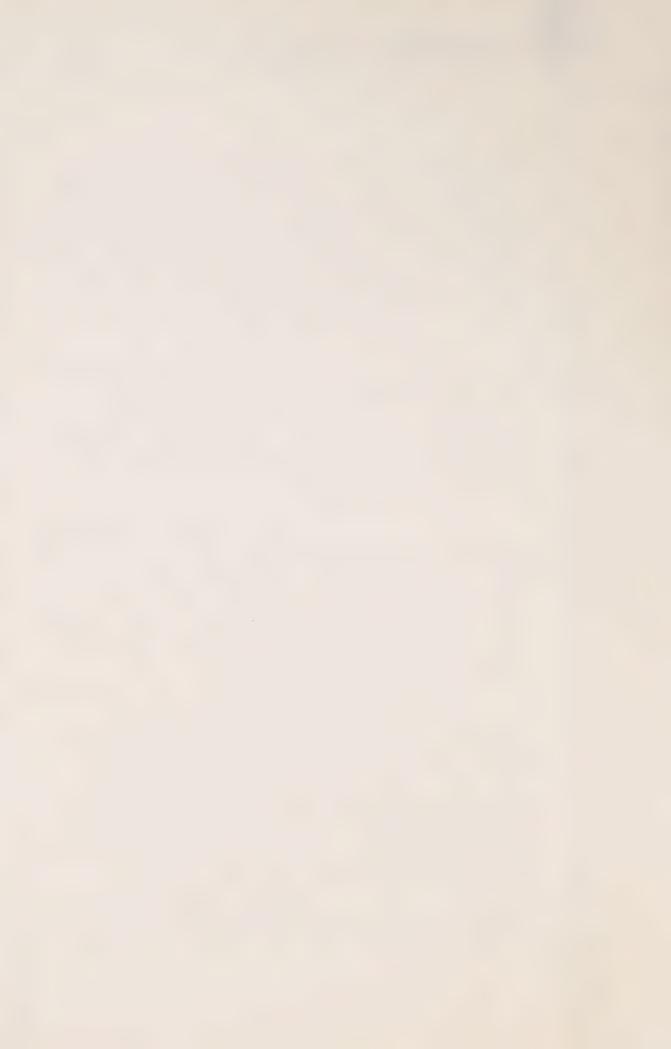
that were tested by Mr. Cimbura are those set out under Samples T30 and T31. T30 appears to relate to Isuprel and T31 is described as fluid alleged to have been taken from the IV of Justin Cook. Were you referring to one of those, Doctor?

A. Yes, I was.

Q. Doctor, what is the source of your understanding that that IV fluid sample, T31, was from the IV bag or what you have chosen to call the volume chamber which has been called in these proceedings the buretrol?

I remember discussing it back a year ago and talking about the source of that fluid and asking some of the staff in the Crown Attorney's office, or Mr. Cimbura, I am not sure which, what the source of that fluid was because I was concerned whether or not it was from the IV tubing itself. I was looking for that information and, as I recall, I was told that the IV tubing was not available to them and this had been obtained from the bag of fluid that was at the bedside at the time. But I can't remember specifically more than that what the source was.

Q. Thank you, Doctor. You have told us, Doctor, that you also considered whether or



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not the drug might have been placed somewhere in the IV tubing below the volume chamber or the buretrol but not close I take it to the patient. Do I have that correctly, that is another possible method of administration?

Well, when I said the distal IV line I meant essentially anything distal to the volume chamber.

> I see, Doctor. 0.

I don't think I have a basis for telling you that it was injected at the needle site or half way up the line or two-thirds of the line. I am not familiar with the IV set-ups that were being used at that time in that Hospital and every company's IV tubing is a little bit different. So, depending on where the injection ports were on the tubing, that would dictate our assumptions as to where the medication could have been injected. But I was assuming it was injected somewhere in the intravenous tubing and then was allowed to infuse into the patient.

All right. Doctor, in the 0. end, and I say this without any suggestion of criticism whatsoever, your estimates are only as reliable I suggest as the assumptions upon which you



base them. Can we agree on that?

A. Yes, I would agree very much with that. I think I may have made that clear in my report that I thought the estimates were frought with potential error. There is a great deal of variability and I think we have to view them as such. But I thought that they fairly represented the outside extremes on both ends of the extreme possibilities. So that then we could say that somewhere between those extremes lay the most probable representation of what actually happened.

Q. Well, Doctor, given the variability which you have said can attach to the situation and the number of unknowns, because we don't know precisely the amount of the dose that was administered nor its time, nor its method of administration, how high a degree of confidence can you in the circumstances place on your best estimate of the amount that was given and the time and the route by which it was given?

A. The best I can say is what I have already said and, that is, that the dose I think had to be something in excess of the half a milligram and was most likely less than the 6 milligrams.



4:30 a.m.

The time of administration in my opinion had to be beyond one hour because obviously some distribution had taken place, and was probably less than three hours, simply because I didn't think the patient would be without critical symptoms of digoxin toxicity given the concentration that were present for a longer time than that.

THE COMMISSIONER: That is more than one hour before death, whenever that was?

THE WITNESS: Before the sample was obtained.

THE COMMISSIONER: Oh, I see. Oh, yes, before whatever time that was.

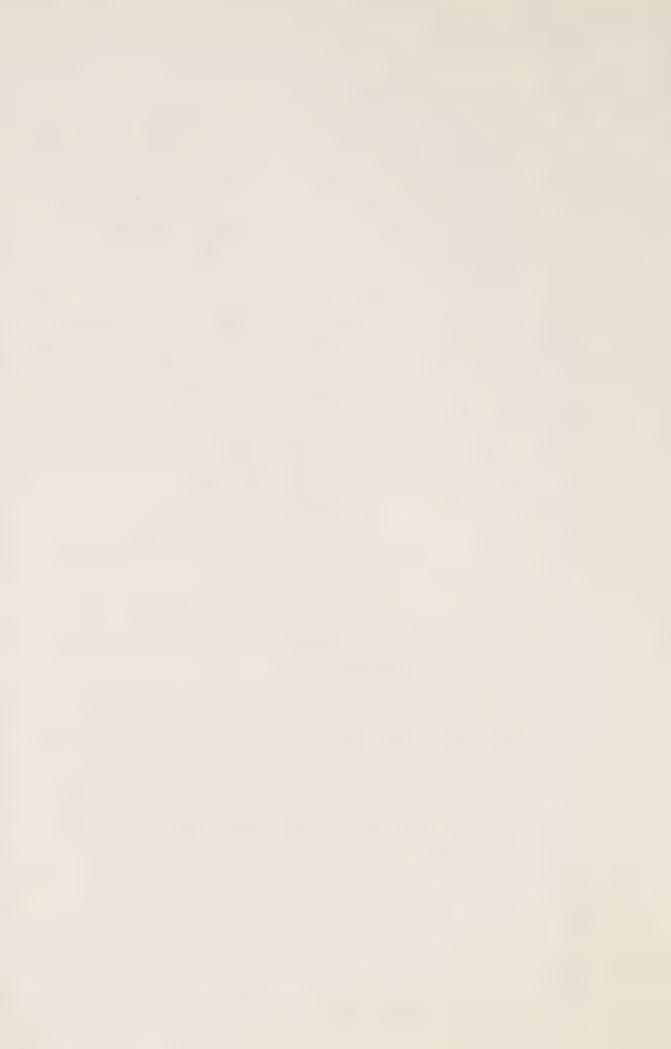
MS. CRONK: Q. 4:30?

A. I think it was obtained at

 $\Omega$ . You are saying then, Doctor, that in your best judgment it was some time before 3:30 in the morning?

A. In my best judgment that is the best I can place it given the data that we have.

Q. Doctor, if we make the assumption, if you will, perhaps that is awkwardly worded, that some of your assumptions are in fact erroneous?







that.

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- $\Omega$ . If not all of them.
- A. I would be the first admit
- Q. Would that in any way affect your conclusion, Doctor, the basic conclusion that you reached that digoxin had with a high degree of probability directly caused the death of this child?

A. No, I don't think my assumption in calculating doses would change that conclusion. I think that given the description of the clinical events that I have seen in the chart and the concentration measurements and the conditions I have been that took place, and the results of those measurements, I think I would still conclude that there was a high probability that digoxin directly contributed to this infant's death.

Q. Doctor, may we turn next if you would please, to the case of Stephanie Lombardo.

Your discussion with respect to this child commences at page 9 of your first reporting letter to Mr. Wiley.

Perhaps, Mr. Registrar, you could give the Doctor Exhibit 78, the medical record of this child.

Doctor, once again in this case you



D3

Doctor.

have previously told us that it is your opinion
that there is a high probability that digoxin directly
contributed to the death of this child; do I have
that correctly?

- A. Where did I say that? I am disagreeing with you, I simply want to ---
  - Q. Page 12 of your report,
    - A. Page 12? Okay.
- O. Is there some doubt in your mind, Doctor?
- A. No, no, I didn't see it in the on page 9 of my -- page 9 of my summary on Stephanie Lombardo, so I was wondering where you were.
- Q. I am referring, Doctor, to the first full paragraph of your Miscellaneous Comments section.
- A. Right, I see where it is, yes, I agree, that is correct.
- Q. Doctor, in respect of
  Stephanie Lombardo, unlike Justin Cook, the only
  digoxin data that is available to us is that from
  exhumed tissues. Can you help us, Doctor, as to
  the basis upon which you formulated the opinion



D4

expressed at page 12 of your report?

A. Yes, I think I can if you will give me just a moment to refer to some notes.

Stephanie Lombardo as you know was referred, was admitted to the Hospital at one day of age and was found to have very severe cyanotic heart disease. I am not sure at which day of age right now, but on the 16th of December she underwent surgery to try to relieve her cyanosis, after which she remained stable but she was - she did remain cyanotic according to the chart. She was sent to the ward called 7G after surgery and was there for several days as I recall, during which time she was described as cyanotic but stable and then was sent to the Intensive Care Unit following that.

She is described in the Intensive Care Unit as good clinical course, pink, good PO<sub>2</sub> which is the oxygen in her blood. She was then, on the 22nd of December, transferred to Ward 4A/4B where she was noted on the chart to be slightly cyanotic. Her electrolytes were normal. She was on no medication except heparin to try to keep her shunt open. She is described as being stable with stable vital signs; feeding one and a half to two



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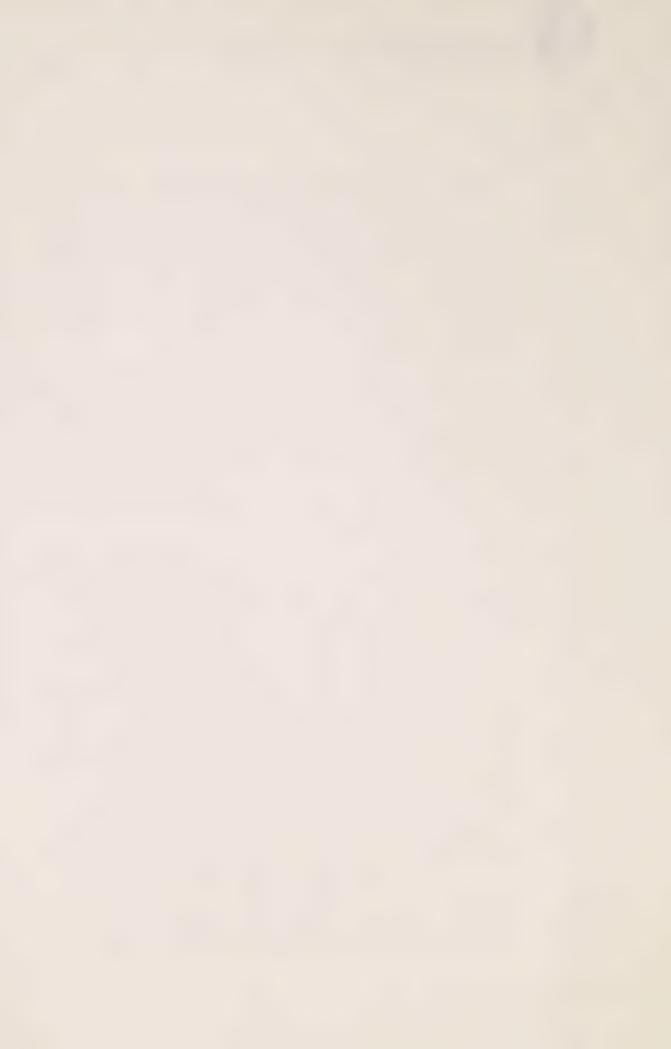
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ounces; a good lusty cry and so forth. So I got the impression from the chart that this child was getting along reasonably well postoperatively for that five or six days in spite of some residual cyanosis, that she was stable and was recovering satisfactorily.

However, suddenly on the early morning of the 23rd of December at 3:30 my note says that she developed an irregular heart, bradycardia, more severe cyanosis, she vomited and then progressed to ventricular fibrillation and had a cardiac arrest at approximately 3:45 a.m.

So one thing that caught my attention immediately was that this child although she had cyanotic heart disease was getting along reasonably well for approximately five days leading up to her terminal events. Then suddenly developed symptoms which could have been related potentially to her underlying heart disease if her shunt had suddenly closed off for some reason or something else happened. Or it is also very typical of digoxin intoxication. So I had to seriously consider that.

The other thing that impressed me was that she was found to have a normal potassium the day before, and the potassium in a sample drawn

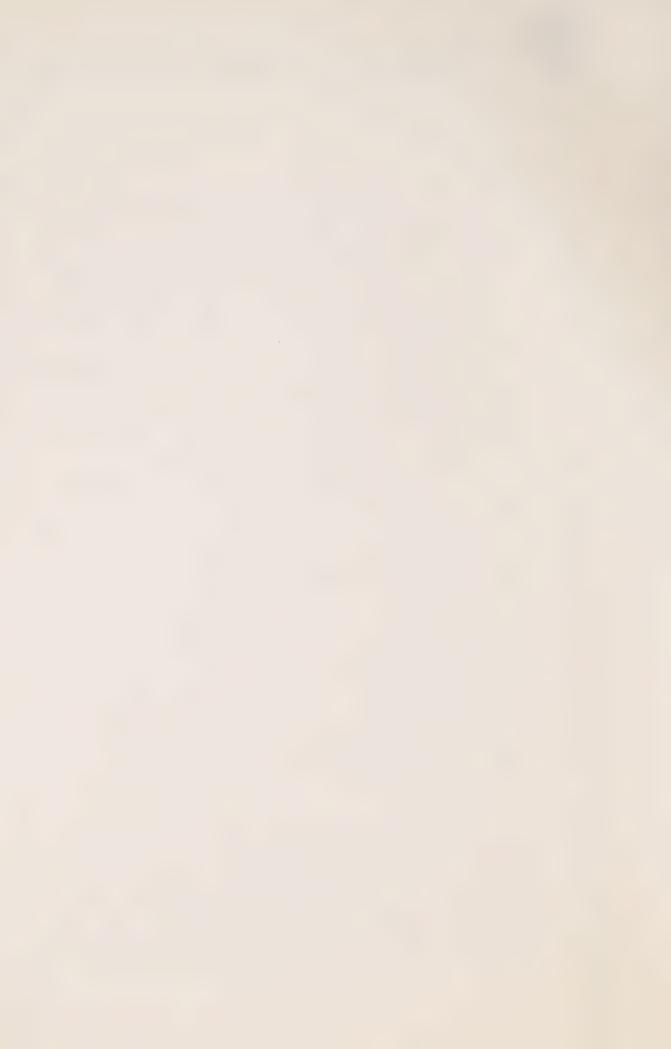


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about 10 minutes into her arrest was 7.4, which is quite elevated. That potassium could be a part of digoxin intoxication. But the compounding factor was that at that time they had just started the resuscitation effort and she had a pH of 7.16, in other words, she was becoming somewhat ascidotic. As you know the resuscitation effort was not successful and she was then pronounced dead approximately 15 minutes later after the initial event.

The other thing that impressed me in this case was that she had never been prescribed digoxin. So we were faced with an infact who was seemingly getting along reasonably well postoperatively for several days; suddenly and unexpectedly developed symptoms compatable with acute digoxin intoxication, with a potassium elevation which may or may not be related to digoxin intoxication because of the compounding variable of the resuscitation and the ascidosis, and in whom digoxin was measured in exhumed tissue.

Because of the clinical events, the description of the clinical events, particularly her clinical course postoperatively and the description of the death event, supported by the presence of digoxin in a baby who had not received digoxin



D7

- -

previously, or at all by record, and the elevated potassium which could have been a part of digoxin intoxication. Putting that altogether I had to say that there was a high probability that her demise was associated with digoxin.

O. Doctor, you have mentioned obviously annumber of factors you considered relevant in this case. You have indicated that in your view the child was doing reasonably well postoperatively and that the terminal events or symptoms that she manifested appeared to have a sudden onset; do I have that correctly?

A. That was my impression from reading the chart, yes.

Q. Dr. Kauffman, Dr. Richard
Rowe of the Hosiptal for Sick Children testified
at length in these proceedings with respect to
these children, including Stephanie Lombardo. He
has indicated in evidence that in discussions at
the Hospital for Sick Children following the death
of the child it was suggested that her shunt had
occluded because no murmur was heard, and that the
shunt may well be clotted off.

Dr. Rowe also indicated that some of the attending cardiologists, specifically Dr. Izukawa



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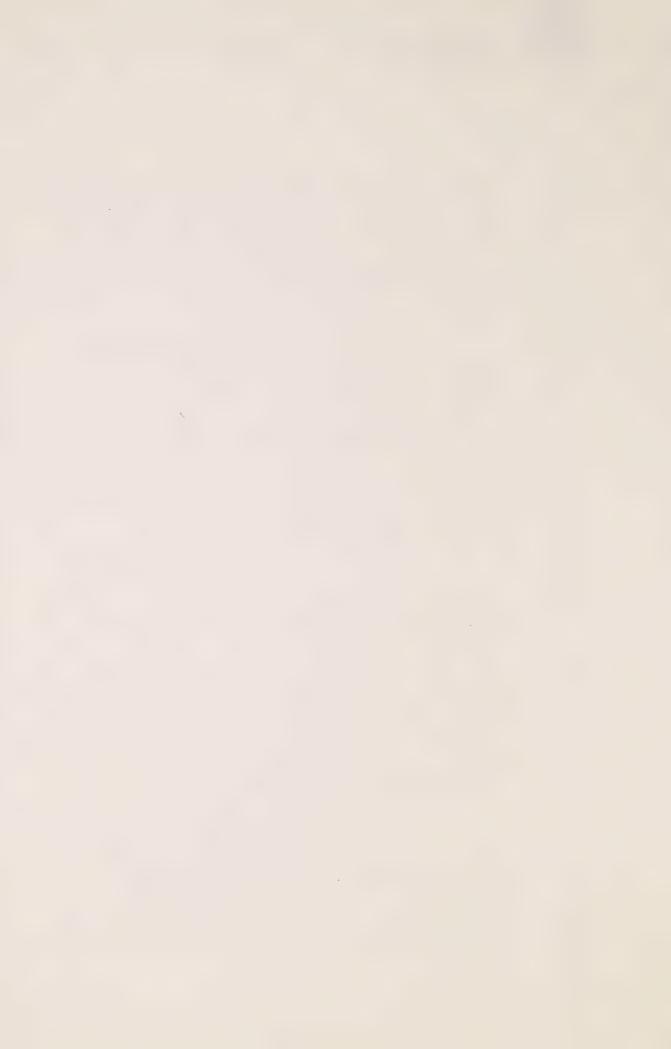
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and Dr. Burns felt that the child was, immediately prior to her death, at immediate risk without any further surgery of any kind. That evidence, Mr. Commissioner, is found in Volume 15 at pages 2558 through to 2561.

Doctor, having regard to that opinion and the opinions expressed by at least Dr. Izukawa and Dr. Burns with respect to her condition immediately prior to death, do those opinions by the attending physicians cause you to alter in any way the views that you have just expressed regarding her clinical course?

I certainly respect those opinions, and I really argue with them. I thought of the same thing when I first read this chart and again when I reviewed it later. I asked a year ago, and I asked again not too long ago whether there was autopsy information as to whether or not the shunt was thrombosed or occluded and apparently an autopsy was not performed on this child.

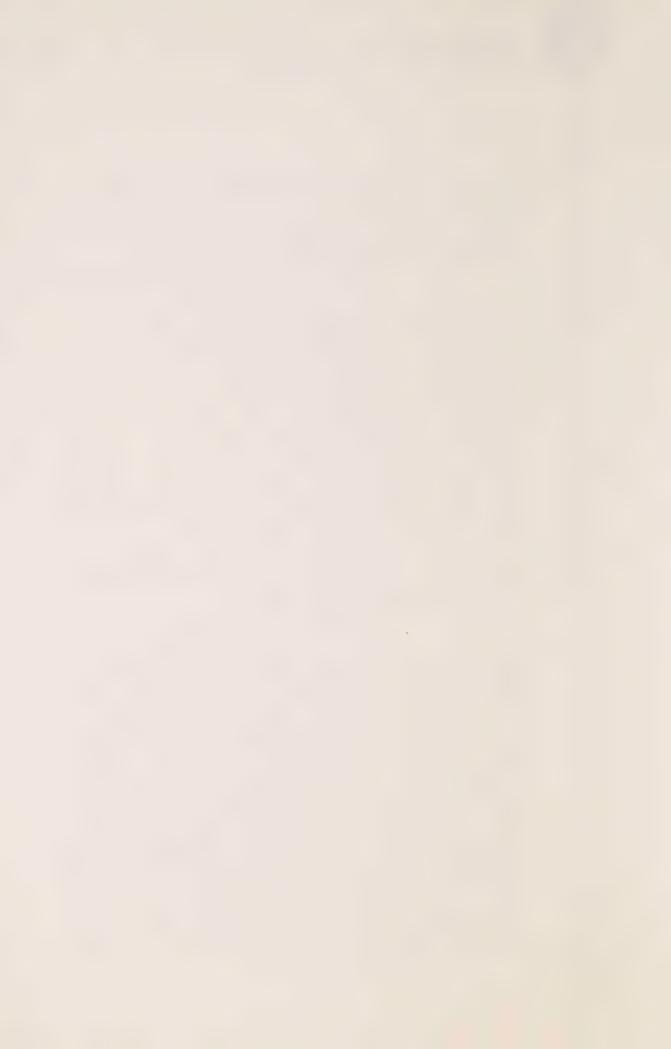
- That is our understanding. 0.
- Unfortunately we don't have that information. I think that that is a possibility because that event could explain the terminal symptoms. But in the absence of objective



evidence that that was indeed the fact I had to strongly consider digoxin intoxication because the symptoms were very typical of that also.

O. Doctor, let me be clear about this. If the shunt had in fact occluded, and I recognize that we don't have any autopsy or pathological findings to assist us in a confirming sense in that regard, but I ask you to assume that it had, all right. If that had occurred, Doctor, of the terminal events that this child suffered, the mode of her dying and the cause of those events, including the nature of her cardiac arrest, consistent in your view, could they be caused merely by the occlusion of the shunt?

A. Yes, I think so, I think they could be. I think that in the absence of digoxin levels being detected in the tissue that would be the most plausible scenario to explain her death even in the absence of an autopsy. The confusing thing is that there was digoxin there which should not have been when she — in the exhumed tissues. It is still possible that that could have caused her death and that she received digoxin also. We can't, at least I can't accept that she did not receive digoxin at some point



prior ot her death. But you could argue that her demise was caused by the blockage of the shunt and that she had simply received digoxin some time in the days prior to her death and that it was there but it had no direct relevance to her death, you could argue that - well, you could argue that now.

My problem with that is I have objective evidence that digoxin is there, I don't have objective evidence that her shunt was occluded; and so that weighing all things as best I could, Ī have to say that there was a probability that digoxin was related to her death.

Q. You are then, Doctor, in assessing those two possible explanations I take it swayed by the concentrations that were found in the tissues?

A. I"m not swayed by the concentrations found so much, although they are fairly high. If you were interpreting in the fresh tissue, but because of the problem of interpreting a concentration in the tissues that I referred to yesterday, I don't think I can place a quantitative value on those, but they do say that clearly digoxin was there and it was there in the tissues and in a number of different tissues it was there in all the tissues in which it was measured.





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So I have to accept that it was there in a child who had never received digoxin, who could have died from another cause; i.e., the shunt occluding, but I have no objective evidence of that. So I guess I have to go -- what I am telling you is looking at all the possibilities I felt I had to make my probability judgment based on the objective evidence.

Q. Well, doctor, we know what you have said, that in the exhumed tissues that were tested at the Centre for Forensic Science at least three of those specimens were tested both on the RIA and the HPLC methods and in addition by mass spectrometry, and levels were found - those were all heart specimens plus chest fluid - and the levels range from 225 nanograms to 667 nanograms.

Do I have it then, doctor, that in your view the only significance that can be attached to the concentrations that were found in the exhumed tissues and in all of the exhumed tissues where it was found, is that it confirms that digoxin was present in the child?

- A. Yes, that is correct.
- Q. All right.

Doctor, you have referred as well to the serum potassium level that was recorded for



this child on the day of her death, a level of 7.4.

Are you familiar with the serum potassium levels that were earlier reported ante mortem during the life of this child?

A. I have looked at those and I have her laboratory sheet here if I can put my hands on it.

 $\Omega$ . Well, to help you, doctor, those levels are recorded in a number of places in the medical chart, but to help you, on the day of her admission to the Hospital the potassium level was 4.

It fluctuated thereafter right through until the day of her death, but on December 14th, for example, it was 6.6.

The next day it was 3.1. By

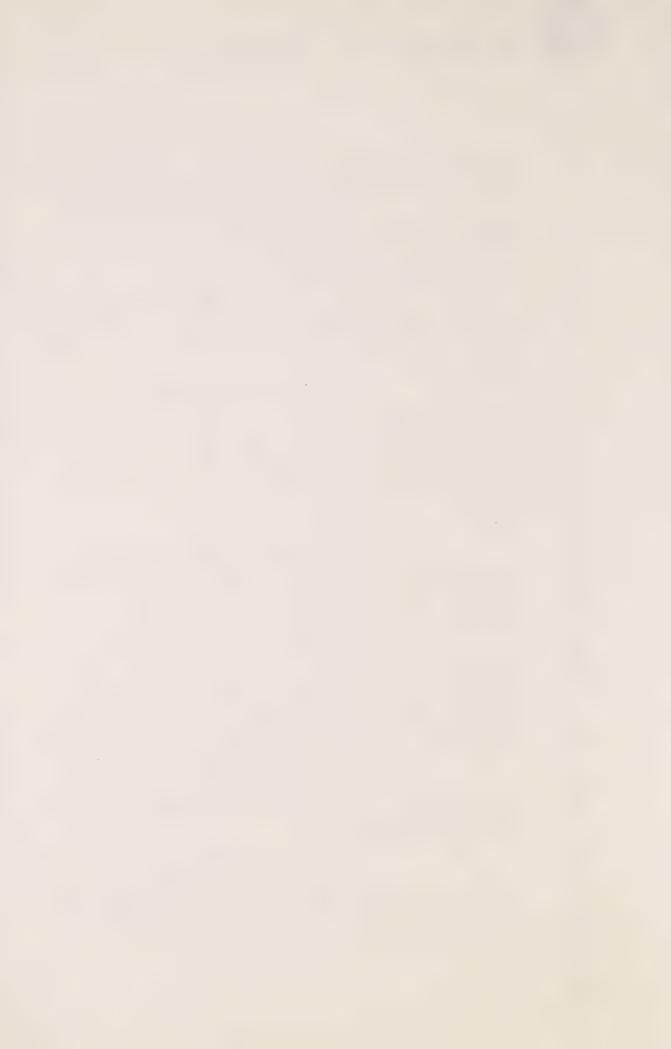
December 17th there were two levels taken: The

first was 3.9, the second 4.6. December 18th it

was back to 5 but then down later in the day to 4.5.

By the time we come to December 21st the level is up to 5.6, but a second reading on the same day showed 3.8.

The day before her death, on December 22nd, the reading was 4.8, and as you have mentioned the reading on December 23rd was 7.4.



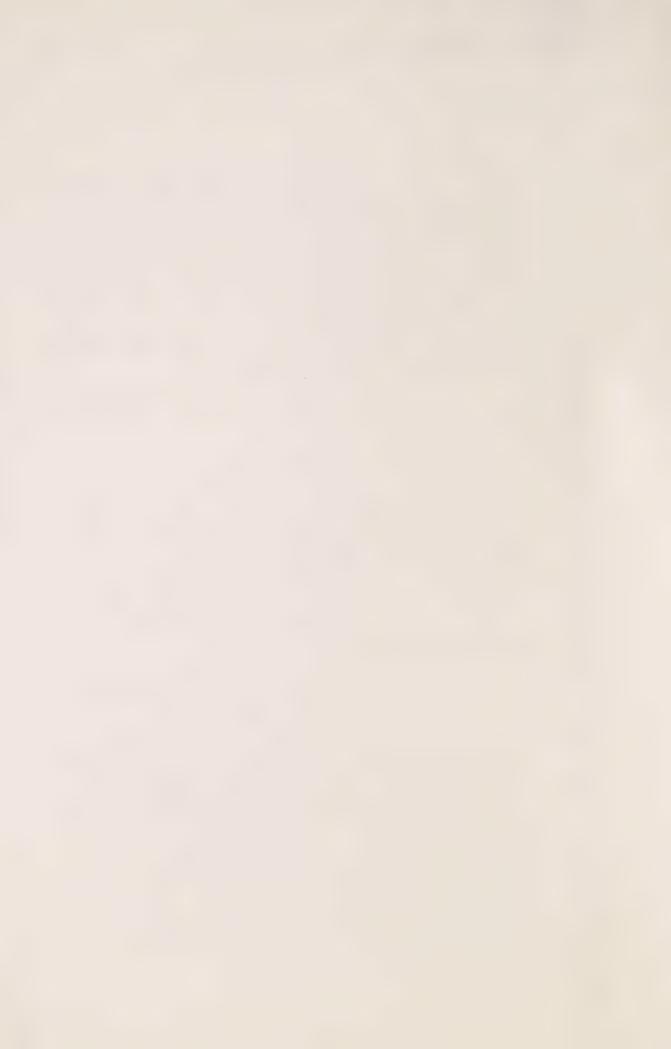
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I suggest to you, doctor, that those levels throughout the history of the child during life indicate that her potassium was fluctuating up and down for that ten-day period. And indeed on at least one occasion reached a level effectively, or at least nearly as high as the one that had been achieved on the morning of her death.

- A. Well, except for the level of
- Q. 6.6.
- A. 6.6, those others I would interpret as fluctuating within a normal acceptable range, and so I attach no real significance to them.

But what was the date of the 6.6?

- Q. December 14th, doctor, the day after her admission.
  - A. Right. That was when she was -
  - Q. Two days old.
- A. And fairly sick and had not been operated yet and was somewhat cyanotic, and I don't know the conditions under which that was drawn either, whether or not it was hemolyzed because hemolysis can elevate serum potassium too. So I would have to look at that one value. But other than that one, up until the one drawn during her



resuscitation it appeared to me that her serum potassium concentration had been essentially normal.

 $\Omega$ . I take it the value of 6.6, though, doctor, is of concern to you?

A. Yes, that would be of concern if it was confirmed. It is not unusual --

THE COMMISSIONER: Would the assayer, if you like, would be know whether the sample was hemolyzed?

THE WITNESS: Yes. Yes, he can usually tell by looking at the serum because it has a pinkish reddish colour to it.

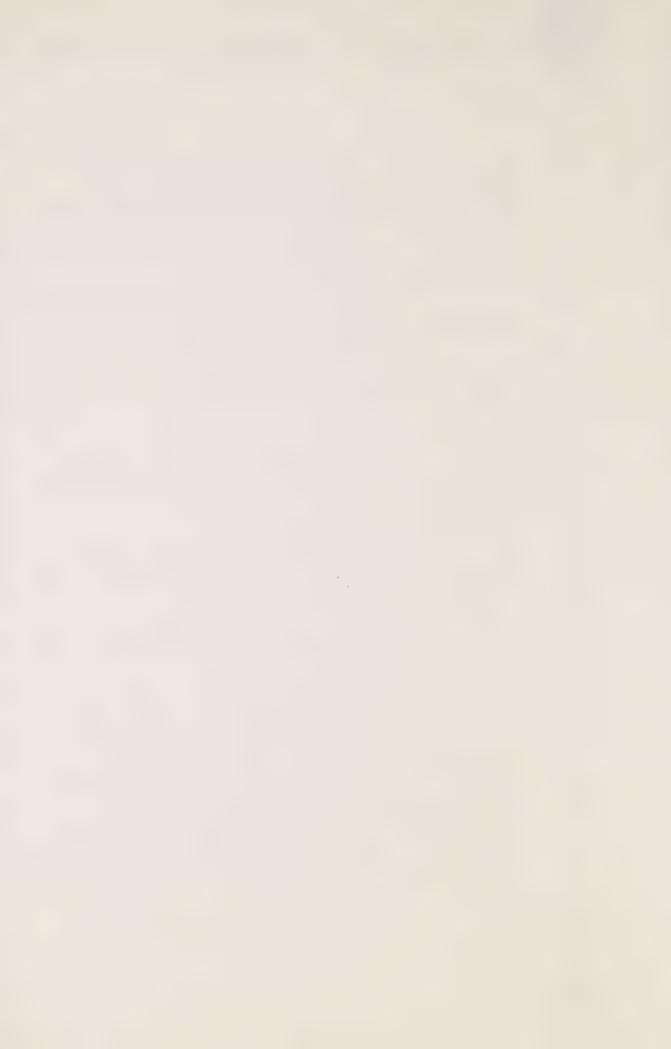
THE COMMISSIONER: Well, quite often they say slightly hemolyzed or something, and I don't think they did in this instance.

THE WITNESS: In the absence of that note I think we have to accept that it was --

THE COMMISSIONER: That it was not?

THE WITNESS: -- that it was a satisfactory specimen, and then we had to look at what was the baby's renal profusion, how much potassium were they receiving in their intravenous fluid, if any, and whether or not it was a consistent change.

I don't attach a great deal of



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medical record?

significance to an isolated elevation of potassium in a sequence of potassium measurements like that. It is not unusual in the patients that I see in the hospital to see in a baby an isolated potassium be high.

What we do when we see that is usually you look at what is the baby's kidney function, what is his other clinical condition, how was the sample obtained, what is his kidney function, how much potassium is he receiving, and then if we don't have -- we usually repeat it also. If it is a consistent trend we have got something real. But if I don't see a consistent trend I usually discount it as not being a real problem.

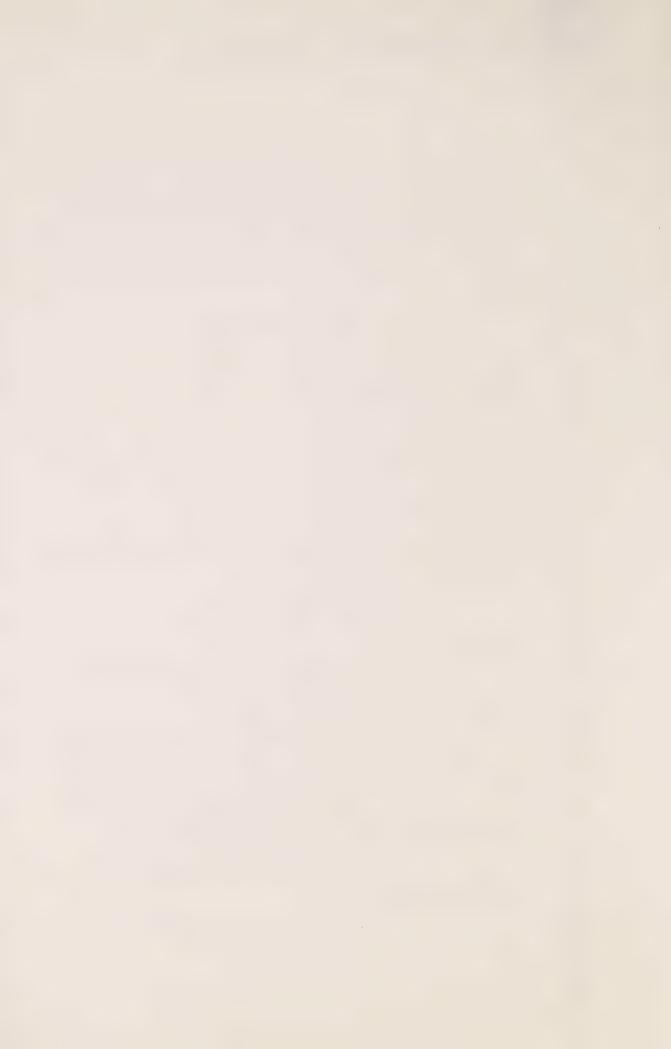
THE COMMISSIONER: I take it back because if --

MS. CRONK: Well, Mr. Commissioner, I was just going to point that out.

Q. Exhibit 78B, doctor, which should be in the medical record that you have there -
THE COMMISSIONER: 78B and it is attached just between pages 97 and 98.

THE WITNESS: What page is the

MS. CRONK:  $\Omega$ . That is the



difficulty. It is an insert, doctor.

THE COMMISSIONER: Just before page 98 on mine. It may have been put in yours the same way.

MS. CRONK: Q. If you look at the third page of Exhibit 78B, doctor, you will see the potassium level taken on December 14th was 6.6 as I have suggested.

A. Right.

Q. But above, two entries above the recorded level is a footnote B, and if we look to the bottom of the page there is an indication that the sample was hemolyzed.

A. Right.

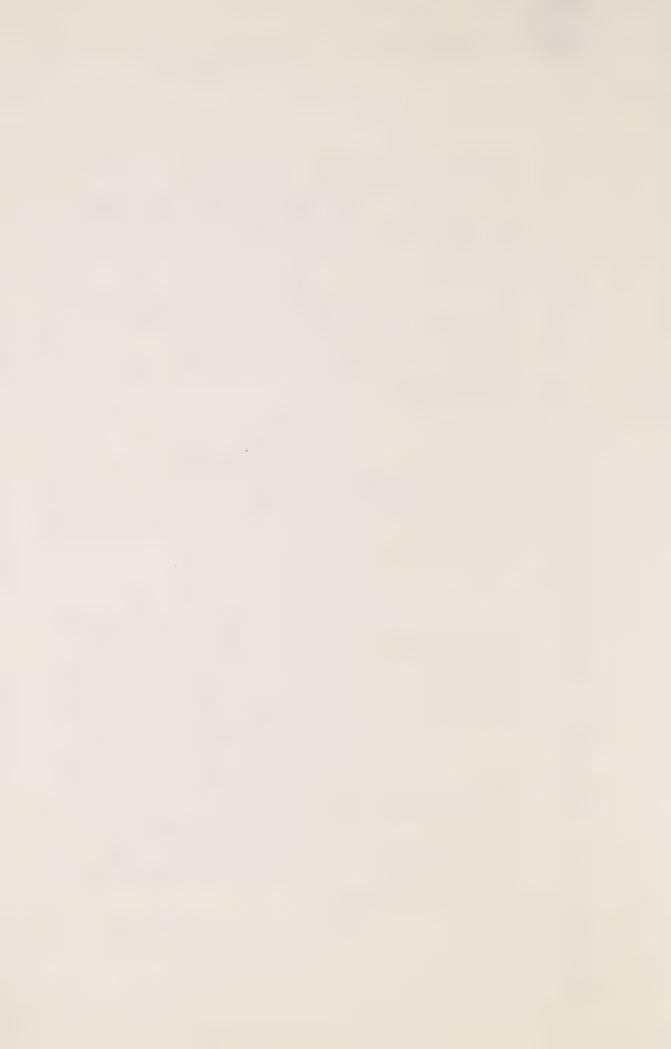
MS. CRONK: Now, as I recall it,
Mr. Commissioner, and I will check this, but as I
recall it, Dr. Ellis' evidence was that all of the
results in a particular column reading downwards --

THE COMMISSIONER: Yes, yes.

MS. CRONK: -- had to be read as applying to the same sample.

THE COMMISSIONER: Yes. Can you tell me something about the hemolysis, how does it affect the potassium?

THE WITNESS: The potassium -- most of



the potassium in the body is inside cells.

THE COMMISSIONER: Yes.

THE WITNESS: Very little of it is outside the cells, so the potassium concentration inside the body cells is in the neighbourhood of 130 milliequivalents per litre. That's the concentration. In serum it is normally around 4 milliequivalents.

When you hemolyze a blood sample that means you break up the red blood cells and they contain a great deal of potassium inside them, and when you break them up it releases potassium into the serum, and this erroneously elevates the serum potassium concentration.

THE COMMISSIONER: How is it broken up? What happens in the process?

that happens is in drawing blood from a small infant like this it is technically difficult many times and frequently it is done by doing a finger or heel stick and squeezing the blood out and collecting it in a capillary tube. In the process of doing that it is easy to crush some of the red blood cells and cause them to break up.

Another mechanism that does this is



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drawing the blood sample through a very small needle which is commonly used if you do a vena puncture in a baby to obtain blood. The common procedure is to use a small gauge needle in the vein and because their veins are so small and fragile pulling the blood through a small gauge needle can break some of the cells too.

Those are the mechanisms that commonly account for this.

THE COMMISSIONER: In any event one would always know?

THE WITNESS: Your laboratory can see this when they separate the cells from the serum. If there has been significant hemolysis some of the hemoglobin in the cells spills into the cells and gives it a pinkish colour.

THE COMMISSIONER: Of course, they separate the cells in order to create serum?

THE WITNESS: Right. Right.

MS. CRONK: Q. Doctor, if that sample had not been hemolyzed I take it there would be a continuing concern in your mind as to what could have caused a level that high?

A. Particularly if it persisted didn't persist, and being aware that it was a and



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16	emolyze	ed	sample	Ι	discount	that	number:	It	is	not
a	a valid measurement.									

Q. Doctor, I ask you to turn to page 101 of the medical record. The next highest ante mortem potassium level I have suggested to you as measured on this child was 5.6 on December 21st.

Do you have page 101?

- A. Yes.
- Q. If you look, doctor, to the column dated December 21, 1980, second to the left, second from the last reading on the right.
  - A. Yes, I see it.
  - Q. We see there the reading of

5.6.

- A. Yes.
- Q. And once again, doctor, we see Footnote A.
  - A. Yes.
- Q. If we look to the bottom of the page it appears to suggest that that sample as well may have been hemolyzed.
  - A. That is correct.
- Q. If we turn to the immediately next page, doctor, we see recorded there two potassium readings: One on December 22nd, the day



before the child's death, the reading was 4.8.

A. Yes.

Q. There is no indication with respect to that sample, doctor, as to whether or not it was hemolyzed.

A. That is correct.

Q. We see the sample to which you have referred us which resulted in a reading of 7.4 on the morning of the child's death, on the morning of the 23rd.

A. Yes.

 $\Omega$ . In this case, doctor, there is a Footnote C. Do you see that?

A. Yes.

Q. And the indication is that that sample was not hemolyzed.

A. That is correct. I assume the laboratory put that note -- I assumed the laboratory put that note there because the level was so high they wanted to make sure that the physicians knew it was not hemolyzed sample to help them in their interpretation.

Q. Well, I can't speak to what they were intending to convey, doctor.

Doctor, assuming as the biochemistry



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the child as to why her potassium level might have been elevated to that extent on the day of her death? As I said, that sample was obtained after her arrest and approximately ten minutes into her --

report has suggested that that reading was not taken

from a hemolyzed sample, is there any explanation in

your view having regard to the clinical course of

- That is right. Q.
- -- resuscitation effort.
- Q. That being the case, doctor, you have told us that obviously in your view you considered that level to be consistent with digoxin intoxication; is that correct?
  - That is correct. Α.
- Absent digoxin intoxication, 0. doctor, is there any other explanation which you as a pharmacologist can posit as to why her serum potassium level might be elevated in the circumstances?
- Yes. I think there is another explanation that one has to consider, and that is that she -- also if you look in that same column, her blood gas measurements, her pH was 7.16; she was quite acidotic, which is consistent with her having shortly before that a cardiac arrest and having



undergone resuscitation efforts.

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Acidosis can cause cells to -potassium to move from inside the cell to outside
the cell because it exchanges hydrogen ions which
are what cause the acidosis. So when you have a
high concentration of hydrogen ions they tend to
exchange into the cell for the potassium and that
forces some of the potassium out of the cell. So
that acidosis could account for elevated potassium.

In addition one has to consider that under these conditions she probably at that point in time was somewhat hypoxic. In other words, her oxygenation was not very good, and she was undergoing resuscitation efforts with some potential trauma to the myocardium associated with that.

So one has alternative explanations for high potassium, and particularly the acidosis I think is significant here. The others are speculative but we do have documented acidosis at the same time.

So I think we have two reasonable alternative explanations: One is potassium was elevated because of acidosis associated with her arrest, and that it could be a part of digoxin intoxication.



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Q. Thank you, doctor.

And, doctor, if we assume for the moment that the potassium level was elevated by virtue of her acidotic condition, I take it we can agree that that could be the case quite independent of any interplay by digoxin?

A. It could be, yes.

Q. Doctor, it is clear from what you told us that on the basis of the information that is available to you, you concluded that this child had clearly received digoxin during her life.

Can you tell me, doctor, or perhaps
I could refer you specifically, doctor, to page 9
of your first reporting letter to Mr. Wiley and
discussion concerning Stephanie Lombardo. You
appear to conclude from the language of your report
that she received a substantial dose of digoxin
either by error or intentionally prior to her death,
and further that the digoxin probably contributed
to her death.

Do you see that, doctor?

- A. Yes, I see that.
- Q. The third paragraph.

Is it your view, doctor, that she received a substantial quantity of digoxin during life?





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Α. Yes. And let me explain my use of the word "substantial" there.

For one, I wasn't selecting words to defend them a year later in another hearing, but I did use the term advisedly at that time. "Substantial" has more than one meaning. It has a quantitative meaning implying a large amount. It also has a qualitative meaning implying not being illusory but being true, real, substantive.





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F BB/cr I was using it in this situation in a non-quantitative sense to imply that I thought that she had truly received digoxin prior to her death and that the measurements that were made clearly indicated that digoxin had been administered.

- Q. Well, Doctor, were you in this case, based on the data that was available to you, able to make any estimates in a quantitative sense as to either the minimum or maximum amount of dose that might have been administered to the child?
- A. No, there really wasn't adequate data to attempt that kind of exercise in this patient.
- Q. I take it then, Doctor, that when you read your report and the references contained in it to the child having received a substantial dose, we would not fairly conclude from that that you were directing your mind to the amount of the drug that she may have received?
- A. No, I intended no quantitative meaning to that word when I used it. I was trying to convey the meaning of it being true or real, the fact that she had received digoxin, a qualitative implication.
- Q. Doctor, whatever the amount of the drug that she received, I take it we can agree on

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the basis of the record that it would have been an unprescribed dose for this child?

- A. That is correct.
- Ω. Doctor, you told me earlier as well that it is possible, I believe you said it could be argued that the child might have received digoxin during her life and that it did not play any part in her death. Do I have that correctly?
- A. I think that is a possibility we have to look at, yes.
- Q. We know in this case, Doctor, that Stephanie Lombardo was admitted to the Hospital for Sick Children on the day of her birth, December 13th, and that she died some 10 days later on December 23rd. Dr. MacLeod has testified before the Commissioner as to his view that an administration of a dose of digoxin to this child at any point in the 10 days prior to her death could account for the concentrations of digoxin found in her exhumed tissues. You know, Doctor, what the concentrations were as reported by Mr. Cimbura. Given those concentrations, Doctor, in your view could the administration of one dose of digoxin at any point in the 10 days in this child's life account for those levels?

MR. SCOTT: I understood the Doctor



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24 25 to say that he couldn't make a quantitative assessment.

THE COMMISSIONER: No, about the amount? He couldn't make a quantitative assessment about the amount that was distributed. But the question is, could at any time, whatever amount was distributed at any time during that period account for the amount that was there. That's legitimate, isn't it. What's wrong with that?

MR. SCOTT: I would have thought it was the same thing. I understood him to say, perhaps he can clear it up for us very quickly, that though he could tell us that digoxin was present in the exhumed tissue and he was able to conclude that it had been administered during life, he was unable to make any comment about the quantities. That was the point of the discussion or the substance.

THE COMMISSIONER: Perhaps he can tell it - perhaps he can tell us, perhaps he can't.

MR. SCOTT: The point I am making is that if he is unable to tell us about the quantities, is it fair to ask him to comment on someone else who has told us about the quantity, who has given their judgment about the quantities.

THE COMMISSIONER: Perhaps the question needn't have been worded that way but the question that



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is being put to him is relatively simple. As far as you know, can you help us, perhaps you can't, as to whether it could do that, whatever dosage was given, was given at the beginning, at the middle or at the end or not?

MR. SCOTT: Well, I like the way Your
Lordship put it, can you help us or can't you?

THE COMMISSIONER: Probably by the
time we get finished phrasing this question you won't
know what it is.

MS. CRONK: But it is improving, Dr. Kauffman, it is improving.

THE COMMISSIONER: If you can help us at all on that question, do, and if you can't, don't.

THE WITNESS: Okay. Do you want to rephrase it before I address it.

MS. CRONK: I think the Commissioner did.

THE COMMISSIONER: What I would like to know from you, without reference to anyone else, can you help us as to whether - how long was this child in the Hospital, 10 days, was it?

MS. CRONK: Ten days, sir.

THE COMMISSIONER: Ten days before death. Can you help us as to whether or not whatever



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dose of digoxin was given to him, could have been given at any time during that period?

THE WITNESS: That is very difficult to answer. Let me back up a little ways and then try to respond to it.

THE COMMISSIONER: Yes.

THE WITNESS: One of the pieces of information that would be helpful in trying to address that would be what was the rate at which this particular infant was excreting digoxin at that point in time. We know that the rate of elimination of most drugs is slower in the immediate newborn period, such as this infant was, than it is when they are three or four or five or six months old or older. So, we have to make some estimates as to what the half life would be in this child. We have a broad range, and we have mentioned that earlier. If you can accept a half life of a day and a half which is the mid range described, middle of the range that is described, or 36 hours, then we can say that in 36 hours after the dose, whenever it was administered, half of whatever was given was gone, only half was left, that is the definition of a half life. In two half lives, or 72 hours, three-quarters of what initially was there would be gone. So, if we can



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accept a half life of 36 hours we can say that in 72 hours very little, at the most a quarter of what initially was there, would be remaining. So, with the kind of concentrations in all the tissues that are described here, given that they are from exhumed tissue, it is hard for me to accept that the dose would have been given longer than three days, let's say, prior to her death. It is virtually inconceivable to me that she could have received a dose 10 days prior to her death and still have digoxin distributed in all these tissues to this degree. That's about the best I can respond to you.

Doctor, two points flowing Q. from that.

MR. HUNT: If I may interrupt before my friend continues.

MS. CRONK: I am sorry.

MR. HUNT: It was my understanding as well that Dr. MacLeod in giving his evidence did indicate that a therapeutic dose given at any point in 35 days preceding death would result in the findings that resulted from the analysis and I took my friend's initial question as being directed to that I think it would be relevant to hear Dr. Kauffman's view with respect to Dr. MacLeod's evidence.



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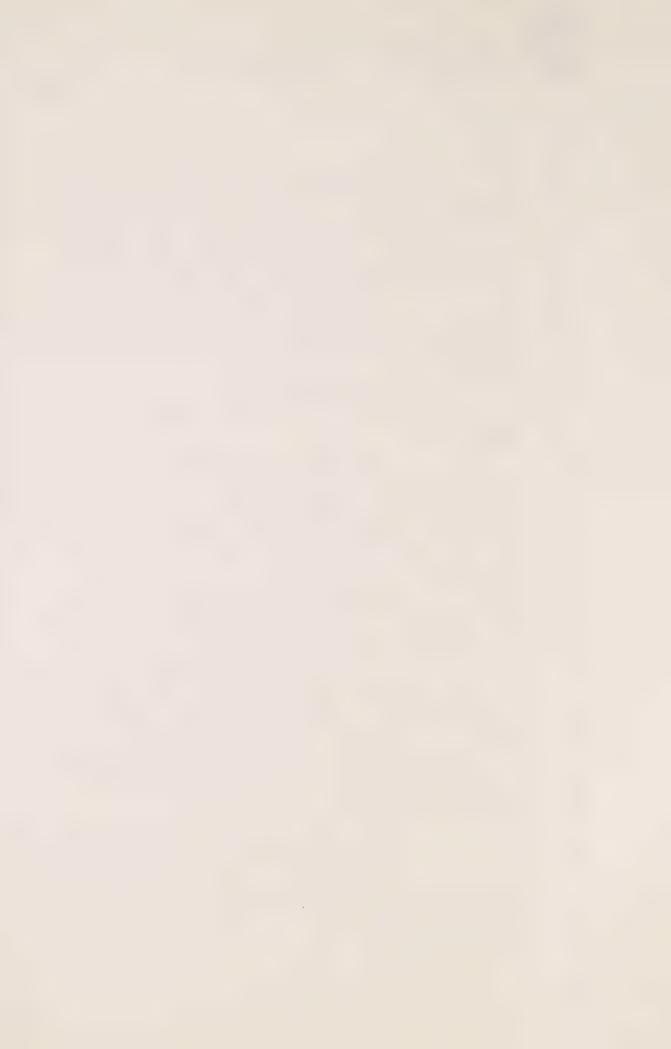
THE COMMISSIONER: I think there is nothing wrong but I think before we do it if it is going to be directly related to what Dr. MacLeod said we had better have the reference.

MS. CRONK: Well, that was the reference I was about to give that Mr. Hunt has risen on.

THE COMMISSIONER: Do you want to read it then.

MS. CRONK: It is found in Volume 64 of Dr. MacLeod's evidence at page 4279. It may well be that Dr. Kauffman isn't in a position to help us with this, sir, but to put it in a context, Mr. Lamek was discussing with Dr. MacLeod three of the four children for whom digoxin had not been administered. He was talking about Jesse Belanger, Stephanie Lombardo and Jordan Hines. The original question was put to him with respect to Jesse Belanger and then following questions with respect to Lombardo and Hines. This was the question on Belanger at page 4279.

THE COMMISSIONER: Well, if you want ---MS. CRONK: It has no meaning, sir, unless I read the one for Belanger and then read the one for Lombardo.



MR. SCOTT: Well, you really have to read about 10 pages, isn't it easier to let the Doctor read it himself.

MS. CRONK: Well, with all due respect, I would like to put the questions to you.

THE COMMISSIONER: You do it whatever way you want.

MS. CRONK: And if you feel it is inappropriate, Mr. Scott, you can make your objections.

THE COMMISSIONER: It might be be better to save the question until after we have dealt with Belanger as well, that's all, but you do it whatever way you want to do it. If you would like to hold that off, bearing in mind that Mr. Hunt is coming right after you and if you want to leave it entirely alone he can handle it.

MS. CRONK: Well, sir, I have no objection, sir, because when I came to Jesse.

Belanger it was my intention to put a like question.

MR. HUNT: Dr. Kauffman isn't our client, sir.

THE COMMISSIONER: Oh, no, I know, but the rules of this game you come next.

MR. HUNT: Based not so much on the rules of the game but the rules of the last witness



that was here we come next.

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THE COMMISSIONER: Yes. Well, I think everybody agrees to that. All right, you carry on now and do whatever you were going to do.

MS. CRONK: Well, we will deal with the matter with respect to the three children at once.

THE COMMISSIONER: All right.

MS. CRONK: I should ask you, Dr. Speilberg - Dr. Kauffman, I apologize - have you read any of the evidence of Dr. Speilberg?

- A. Yes, I have read part of it.
- Q. Have you read the part which pertains to the possible administration of digoxin to these three children, that is, Stephanie Lombardo, Jesse Belanger and Jordan Hines?
  - A. I believe I have.

Q. All right. Doctor, you have told us two things with respect to Stephanie Lombardo, as I understood it. One of the pieces of information you said which you needed was to know the rate of elimination from the child in order to answer the question that was asked of you. You have, however, told us that the rate of elimination is usually slower in the newborn period. Do I have that correctly?



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- This child, Doctor, we know was only 10 days of age at the time of her death. Can we reasonably infer from that that her rate of elimination would be much slower, for example, than a child who might be 30 days of age, or a child who might be two months of age.
- All other things being equal that would be a fair assumption, yes.
- And as well, Doctor, you told me earlier that quite apart from the issue of age that the rate of elimination that might apply to a newborn could as well be influenced by the renal function, the kidney function of the child. Do I have that correctly?
  - That is correct.
- 0. All right. Was there in this case, that is, the case of Stephanie Lombardo, Doctor, anything which you perceived on the basis of your review of the medical records to suggest that she was suffering from any degree of renal impairment or kidney difficulty?
- Let me refer to her laboratory the sheets that I have. The usual measure of kidney function is the blood urea nitrogen which is indicated by BUN on the laboratory sheet.



Kauffman, dr.ex.
(Cronk)

Ω. I am sorry, Doctor, are you referring to a particular page in the medical record?

A. Well, that is what I am referring to. I am referring to some copies I made myself of the laboratory sheets. Maybe I should use the medical record. Can you refer me to the ...

THE COMMISSIONER: Reference is at 102 and at 100 and also Exhibit 78B.

THE WITNESS: On Exhibit 78B on the column labelled 13 December there is a BUN result given as 10 I believe.

A. On Exhibit 78B, the right hand column.

Q. Yes, I see, Doctor.

A. There is a BUN value reported as 10. That is within a range of normal for a newborn. On page 100 under the column 18 December there is a BUN reported of 7, which again indicates normal newborn renal function.

On page 102 on 23 December there is a BUN report of less than 5, which again is acceptable as normal.

THE COMMISSIONER: I am sorry. How could



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less than 5 because less than 5 could be zero.

THE WITNESS: Well, surprisingly sometimes the newborns have reported zero.

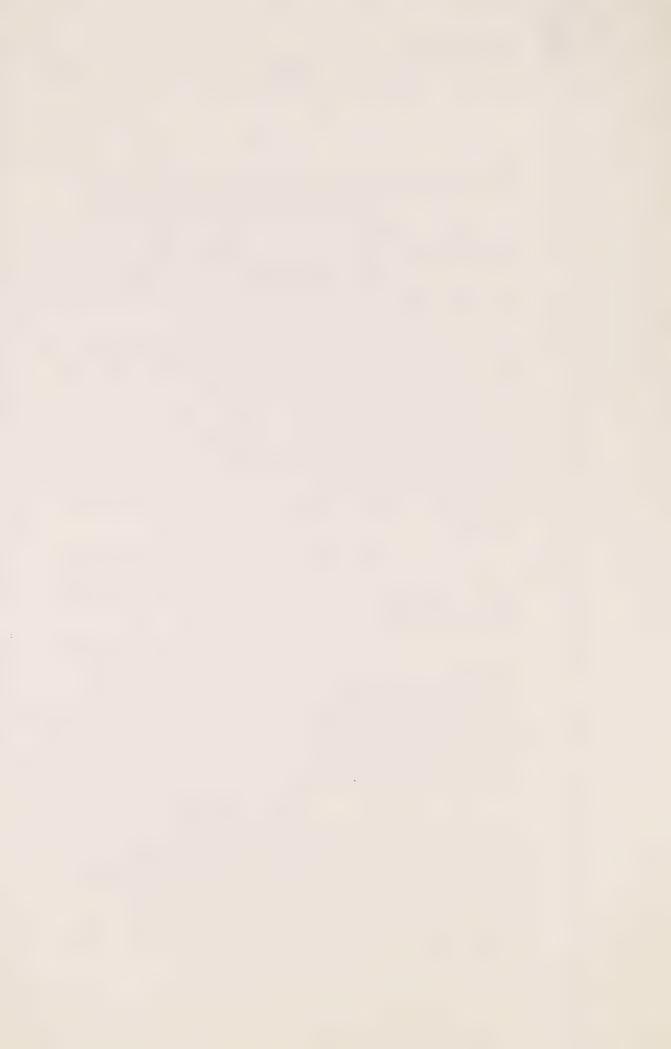
THE COMMISSIONER: Oh, I see. It is the high one that we worry about?

THE WITNESS: Yes, it is the high one you worry about. If it is above 18 or 20 then you start suspecting that the kidneys aren't working as well as they should. So, in answer to your question, looking at the laboratory results, I see no evidence in this baby that there was any compromised kidney function.

MS. CRONK: Q. Are the BUNs, Doctor, in your judgment, the major indicator of the state of renal functioning?

This is the major piece of Α. information available on these sheets, yes. Corollary supportive information is the fact that the potassium was normal throughout this time until the latter sample was drawn.

Doctor, you have told us that you were able to in this case based on the information available to make any calculations concerning the possible dose of digoxin that may have been administered to the child. You did however comment



in your report, as I understand it, as to the



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possible route of administration, is that correct? I refer you to page 9, Doctor, in the last paragraph of your report.



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A. Yes, I did.

Q. You indicate:

"Because of the condition of the infant it is more likely the dose was administered intravenously rather than orally."

Do you see that, doctor?

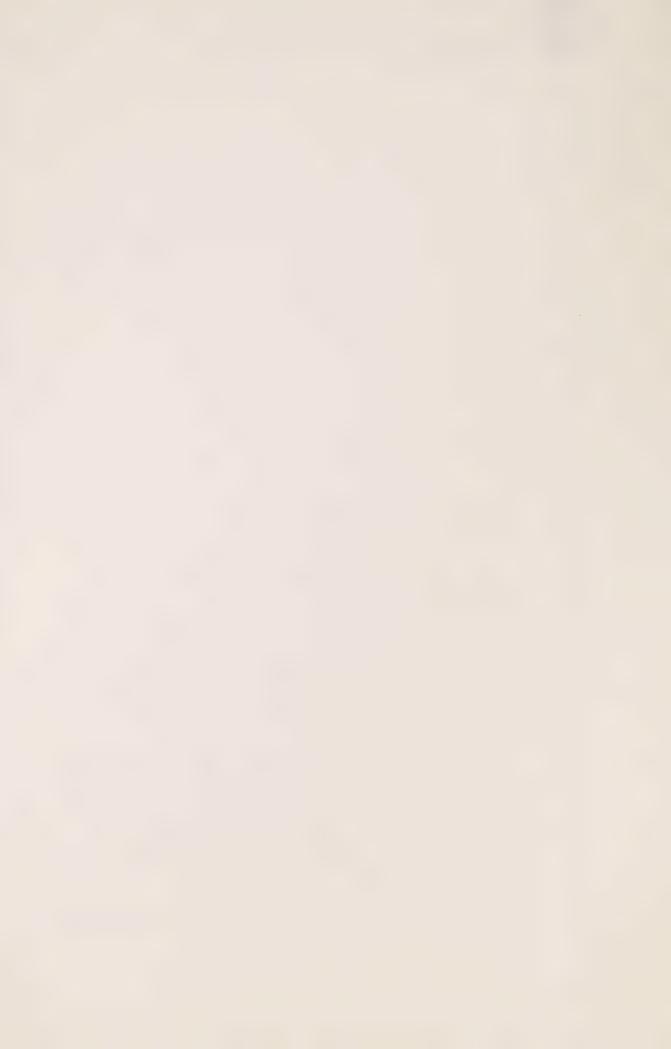
A. That is right.

Q. Can you help us, doctor, as to the basis upon which you reached that conclusion?

A. I think the reason I said that was that I felt that because of her cyanosis, some minimal problem feeding, occasional vomiting and so forth, it would be somewhat difficult to get an excessive dose of digoxin into her orally. I thought since she had an intravenous line running that it would have been easier if it was given to her, if administered by that route. I think that is why I said it was more likely.

Q. I take it then, doctor, that on the basis of the information that is available, and recognizing the data that we do not have, it is as well entirely possible the dose could have been administered orally to this child?

A. Yes, I think that is possible.



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I was simply trying to give a feeling - in my judgment at the time between those two alternatives what the more likely one was, but I think it could be possible to give it orally.

Doctor, may we turn then to 0. the case if you will of Jesse Belanger. Once again in your miscellaneous section of your report you have expressed the opinion that there was a high probability that digoxin intoxication contributed directly to the death of this child, that is at page 12 of your first reporting letter, doctor. As I have asked you before, I would in this case ask you the basis upon which you formulated that opinion.

Here again was an infant who was admitted shortly after birth, at two days of age with severe cyanotic heart disease with a single ventricle and a hyperplastic artery going to the lungs. He had a shunt placed to try to relieve the cyanosis several days after he was admitted, on the 23rd of December, and again was transferred to 7G from the Intensive Care Unit.

This child also had some persisting condition, his heart problem, post operatively had some persisting lung problems which were as near as I can tell from the chart causing problems up to the time of





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his death. He had, when he arrived on the Ward 4A/B on the 28th of December, five days after surgery, decreased air entry into the left lung. He was reported to have right upper lobe atelectasis and I think some left upper lobe atelectasis. He had what were described as adventitial breath sounds and streaking in the upper lobes on x-ray. He had a lot of difficulty with his caloric intake. His urine output was described on the 26th of December as being low. It was necessary to feed him by a feeding tube because he was not feeding well. Then suddenly on the 28th he was described at 1830 as having an irregular heart rate, being dusky, his respiration suddenly went up and became, up to 80 and became shallow and this was during the tube feeding. His heart rate decreased and then he had a cardiac arrest and underwent resuscitation efforts. This was I believe approximately five hours following his transfer from 7G to 4A/B.

Again one of the impressive pieces
of information in this infant that he was not
prescribed digoxin any time during his life. However,
he did have digoxin present in his liver and a
sample of skeletal muscle and exhumed tissue. The
concentration I believe reported in skeletal muscle



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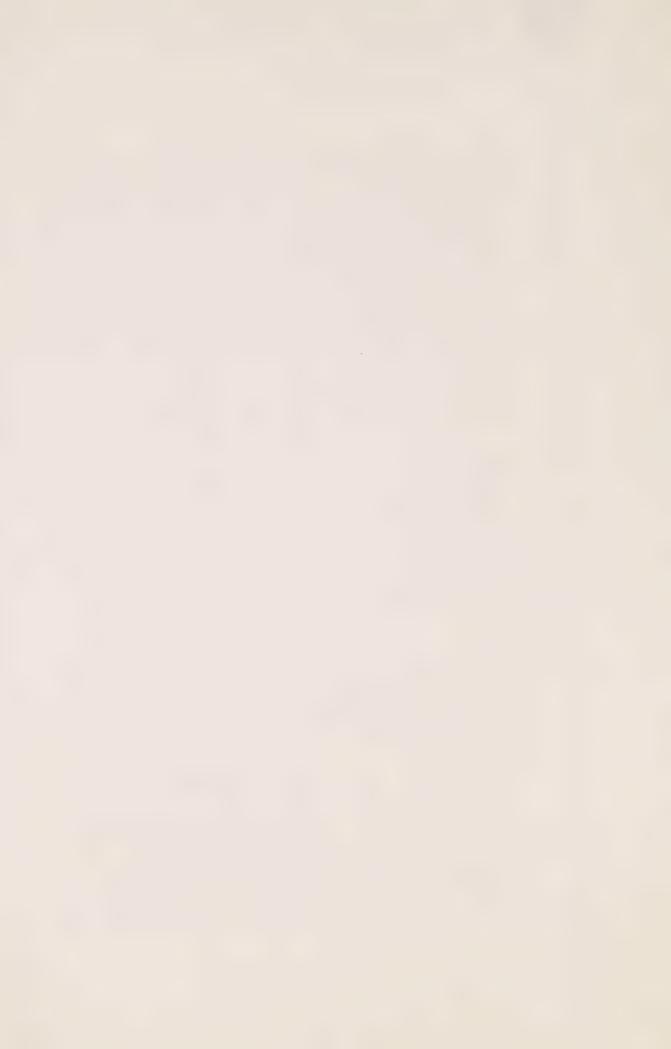
was 43 nanograms per gram, and in liver it was 253 nanograms per gram. The only abnormal laboratory values that were recorded were an elevation of the blood urea nitrogen and a drop in his calcium concentration in his serum on or about the time of surgery, but these returned to normal long before his death. So that at the time of his death I saw no evidence of decreased kidney function and his calcium concentration was back to normal.

My judgment on this child that he probably died as a result of digoxin again was based on the description of the events surrounding his death, the clinical description and the presence of digoxin in his tissues when he ostensibly had never received digoxin during his life.

Q. Thank you, doctor.

With respect to the concentrations found in the tissues of this child, once again we are talking exclusively about exhumed specimens isn't that correct?

- A. That is correct.
- Q. And the concentrations that you have indicated in the liver specimen was 253 nanograms, and in skeletal muscle 43 nanograms according to Mr. Cimbura's toxicology reports. Do



those concentrations, doctor, in this case tell you, or help you to draw any conclusions other than that digoxin was present in the body of this child?

A. No, again that is really all we can say in terms of the digoxin itself is that it was there when it shouldn't have been.

Q. Do they assist you in any way, doctor, in assessing whether or not digoxin intoxication contributed to this child's death?

A. Not by themselves, no.

Q. Was there any other feature, doctor, other than the clinical condition of the child that you have described, that in your view was helpful to you in reaching your assessment that digoxin intoxication had probably played a part in this child's death?

A. No, I really didn't have any objective evidence other than the description of the terminal event in the chart.

Q. So I take it, doctor, we are really talking about simply those two things; first of all the presence of digoxin as confirmed in your view by the concentrations in the exhumed tissues.

And secondly, the terminal events in the chart?

A. Yes.



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	$\Omega$ . Doctor, with respect to the
terminal	event sustained by Jesse Belanger, was there
anything	upon which you placed particular significance
arriving	at the conclusion which you reached?

- A. Pardon me a moment while I get some notes, I may be able to answer you more succinctly that way.
- Q. As well, doctor, the medical record is Exhibit 79 should you care to have reference to it.
- A. In general it is what I just said; from reading the medical record it appeared to me that the death was sudden; it was somewhat unexpected; and that the symptoms described in the chart were those consistent with a digoxin-induced death. I am looking for -- to answer you more specifically in terms of the actual symptoms I will have to refer to the -- see if I can find the description of that event in his chart.
- Q. Well, doctor, it is approaching the time when perhaps we can take our morning break.
  - A. Okay.
- Q. And I would ask you if you -THE COMMISSIONER: You always seem
  to find some way to destroy the benefit of the break



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for the witness, but I hope you won't be too long in sorting that out.

 $\mbox{MS. CRONK: } \mbox{$\Omega$. Perhaps if you look}$  at the progress notes.

 $\hbox{A.} \qquad \hbox{I will look it up and see if}$   $\hbox{I can locate the progress notes.}$ 

MS. CRONK: Thank you.

--- recess.



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--- Upon resuming.

THE COMMISSIONER: Yes, Miss Cronk? MS. CRONK: Q. Dr. Kauffman, have you had a chance to look at the medical record of Jesse Belanger over the break?

A. Yes, I have had a chance to refresh my memory and look at parts of the charts.

O. Doctor, can you tell me then, please, what features in the clinical course of this child or what features amongst the terminal events led you to the conclusion which you reached regarding the involvement of digoxin?

A. If you turn to page 58 of the chart --

> Yes, Doctor. 0.

A. We start seeing the notes written two days prior to his death, and I suppose we can go back earlier than that, but I didn't select to do so because I think this is consistent. He was over - approximately five days after his surgery was - I believe or am I wrong about those dates?

THE COMMISSIONER: December 23rd? THE WITNESS: I think it is correct. He was operated December 23rd and he died December

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28th, so during those five days on the several wards he is consistently described as stable and doing well.

For example, at the bottom of page 58 of the medical record on 26 December a note is made that the shunt murmur is present with both systolic and dystolic component; the oxygen has increased.

On page 59 and if you want to look at a - if you want to bring up anything else that is fine. In am just pointing out the highlights.

Q. I am still here, Doctor.

A. Okay. Sinus in the midpage 59 there is a note that is cardiac status,
sinus rhythm rate is 150 to 175, blood pressure
88 to 100. His urine output was low at that point
but his cardiovascular status was fine and stable.

Later on the 26th he is described as being in no distress although he was having respiratory symptoms, but in spite of his atelectasis he seemed to be stable and doing well.

On 27 December he was transferred from the ICU because of a bed shortage, and the note is that he is doing well this a.m., 40% oxygen and that they will transfer to 4A when his breathing problem is resolved.



A note on December 27 on page 61, stable and 40% oxygen, slightly cyanosed.

Further down the page, December 28, taking his 5 - I don't know if that is 5 or 50 - probably 50 cc of SMA12, his formula, by tube. He was being tube fed.

Further down the page, 14 to 1930 on 28 December he is described as being pink and oxygen. Feeding tolerated well.

On the next page 2812 on his transfer note it says in no distress; no acute distress.

No evidence that he is unstable.

The note on the top of page 64 on 28 December, 1300 to 1900 hours, stable during the afternoon; apex 134 to 170 regular. Tube fed at 1400 and retained. Colour remained pink.

to be irregular; dusky, respiration suddenly increased to 80 and shallow. Colour extremely poor. His apex dropped and he sustained a cardiac arrest. And then the arrest and resuscitation note follows with a description of their efforts at establishing a sinus rhythm. Their inability to re-establish normal heart rate with normal cardiac output and eventually



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unsuccessful resuscitation.

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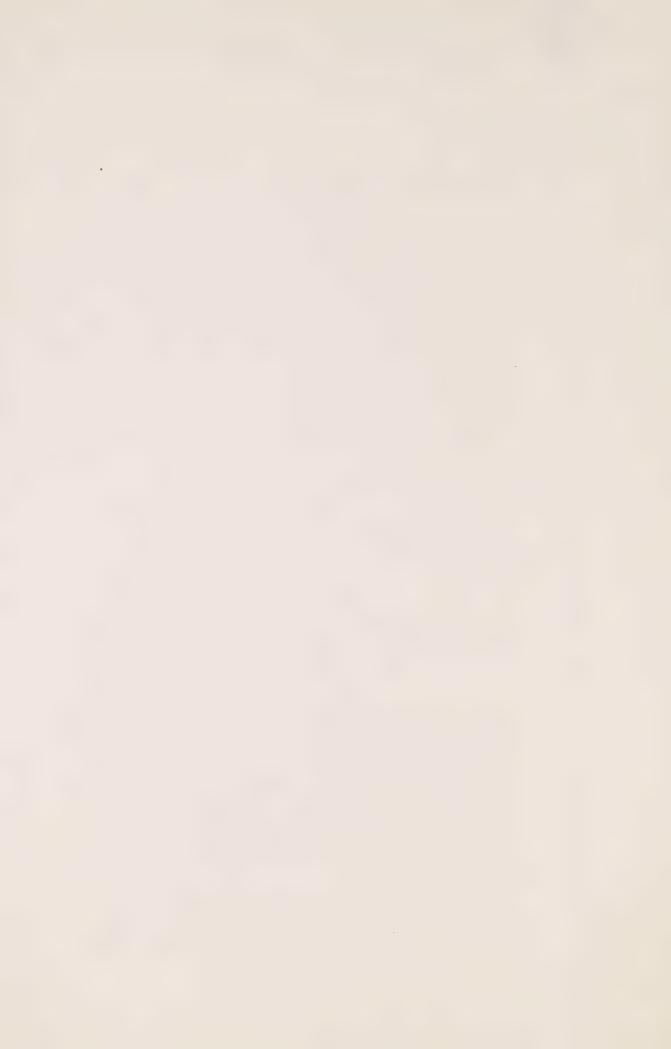
so the picture painted by the medical record is that of a baby of five days post op who had some lung atelectasis, but in spite of that was stable, seemed to be coming along satisfactorily. You don't get the impression from this record that anything unusual was expected, and suddenly for no apparent reason he is in trouble with bradycardia, a cardiac arrest and can't be resuscitated.

That means that something very different suddenly happened other than what was going on prior to 1830 hours on 28 December.

If you turn to page 150 in the medical record you will see that his blood gases confirm that he was doing well cardiovascularly.

If you look on page 150 in the column dated 26 December, which is second to the left in the right hand margin, you can see that his pH was 7.33 which is normal and his PO<sub>2</sub>, his oxygen was 31 which is satisfactory for a baby in this condition, particularly if it is a capillary blood sample.

On the next column, 27 December, at 0730 in the morning, an arterial sample, his pH



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again is normal. His  $PO_2$  is satisfactory and 40% oxygen.

on 27 December, his arterial blood gas, again the pH is normal. A little bit alkalotic, but that is okay, and his  $PO_2$  is even better. It is coming up. It is up to 68 now and 40% oxygen.

And at 8:00 on 28 December on the same page his pH is still okay. It is a little bit alkalotic but that doesn't bother me, and his PO<sub>2</sub> is 43 and he is doing well enough that they have reduced his inspired oxygen concentration by 9%. So everything is pointing to a baby who is convalescing satisfactorily, and suddenly has a catastrophic event resulting in death.

Doctor, amongst the features that you have outlined for the several days prior to the child's death on the 28th of December, we see as well, do we not, a continuing condition of cyanosis?

A. That is correct. That

doesn't bother me because with his underlying

heart disease and a shunt described as being

4 millimetres, all that means is that the shunt

did not provide a high enough pulmonary blood flow



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to get his oxygen up to the normal range. But he did improve over his pre-operative condition and he did seem to be stable.

Q. Well, Doctor, in addition to this ability which you have noted in your judgement and as well the cyanosis, we do see reflected in the progress notes several days prior to his death continuing respiratory difficulties from his collapsed left lung, do we not?

A. That is correct. He is described as having x-ray changes and showing atelectasis. Noisy breathing when he is listened to with a stethosope, but his respiratory rate really was not particularly elevated, and this did not seem to be a progressing problem. It was problem but it was not an acute problem that was apparently causing him a a great deal of difficulty.

Q. And that continued to be the case, Doctor, I suggest, until the death of his day.

A. That is correct.

And as well, Doctor, amongst, the terminal symptoms that are disclosed by the progress notes we see that the child experienced as you suggested an irregular apex, dusky colour,



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respirations became shallow, experienced bradycardia, gasping, successive arrhythmias.

Could all of those terminal events,

Doctor, in your view have been fully accounted for by
the child's underlying cardiac condition and disease
state.

A. Well, again this is a child who had severe cyanotic disease, who had a shunt placed at surgery five days earlier, and had the shunt become obstructed, that kind of catastrophic event could produce these kinds of symptoms.

They are also symptoms totally compatible with digoxin toxicity.

For that reason it is important to look at - he did have an autopsy and so I turned to see what the autopsy showed in terms of the shunt. If you turn to page 19 of the record the report, anatomical diagnosis at the end of the autopsy report, page 19 of their record,

"Status Blalock-Taussig Anastomosis,
retroesophageal subclavian artery to
left pulmonary artery, Anastomosis intact
and patent."

That means it was open and working and okay.

Q. Yes.



	Α.	So we kno	ow in thi	s baby	the
catastrophic e	event was	not relat	ted to a	shunt.	That
makes it even	more like	ely that	it was di	goxin	
related.					

Q. Well, Doctor, perhaps my question was put to you badly.

Leaving aside the question of occlusion of the shunt, which appears to have been ruled out by the findings at autopsy, could the child's cardiac condition per se have accounted for those terminal events?

A. I suppose it could in a general answer.

I see no evidence in looking at the record that there was any hint that anything was changing to make him less stable at five days post operatively.

Q. Doctor, as well in this child according to the autopsy report there were findings suggestive or indicative of partial Di George's Syndrome. Did you note that on your review of the autopsy report?

A. I noticed it, yes.

Q. All right. Given that feature, Doctor, and as well the cyanosis that we



again?

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referred to and the continuing respiratory difficulties
putting those all in context, do you agree or dis-
agree that all of his terminal events and method of
his dying are equally consistent with his underlying
cardiac condition?

A. Will you go through that all

Ω. All right. Bearing in mind that this child was found to have had partial Di George's Syndrome.

A. Right.

 $\Omega$ . Bearing in mind the cyanosis that he was experiencing and the respiratory difficulties he was experiencing prior to death.

A. Right.

Q. Bearing all of that in mind, Doctor, do you agree that his terminal events and the method of his dying are as equally consistent with his underlying cardiac condition as they are with digoxin intoxication?

A. No. My interpretation would be that they are more consistent with digoxin intoxication than a catastrophic event from any of these other causes although I have to say that these other anomalies including his cardiac anomaly could



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have resulted in death at some time, but looking at the description of his course up to the time of his death I see no evidence that things were changing or that there was any hint that he was deteriorating in any way to suggest that this event might have occurred at that particular moment in time.

Q. Thank you, Doctor.

Doctor, we know that this child was admitted to the Hospital on November 19th, and as you have pointed out he died on December 28th. That is a period of some 35 odd days at the Hospital for Sick Children.





this:

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In Dr. MacLeod's evidence before this Commission - this is found, Mr. Commissioner, at Volume 64 commencing at page 4273, he produced a paper, Doctor, an article which had to do with the elimination of digoxin from the body and he said

"A. The point that I wanted to make with this paper was that, once digoxin is administered in a therapeutic dose or in a super therapeutic dose, it is bound in a variety of tissues and simply will not disappear from those tissues within a predictable time frame. All the times that you have heard in this hearing refer to disappearance from the plasma space, and that is a different animal than talking about disappearance from tissues.

Q. Let us be clear on that, Dr.

MacLeod, because I confess it is a matter
about which I was totally confused.

No doubt the confusion was mine alone
and everyone else understands it.

We have heard about elimination half





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"life and we have been told that that can be a period of anything from 20 to 80 hours and, in the course of 5 of those half lives of whatever length they may be, you will have essentially limited whatever it is - 97 per cent or 99 per cent - of the digoxin.

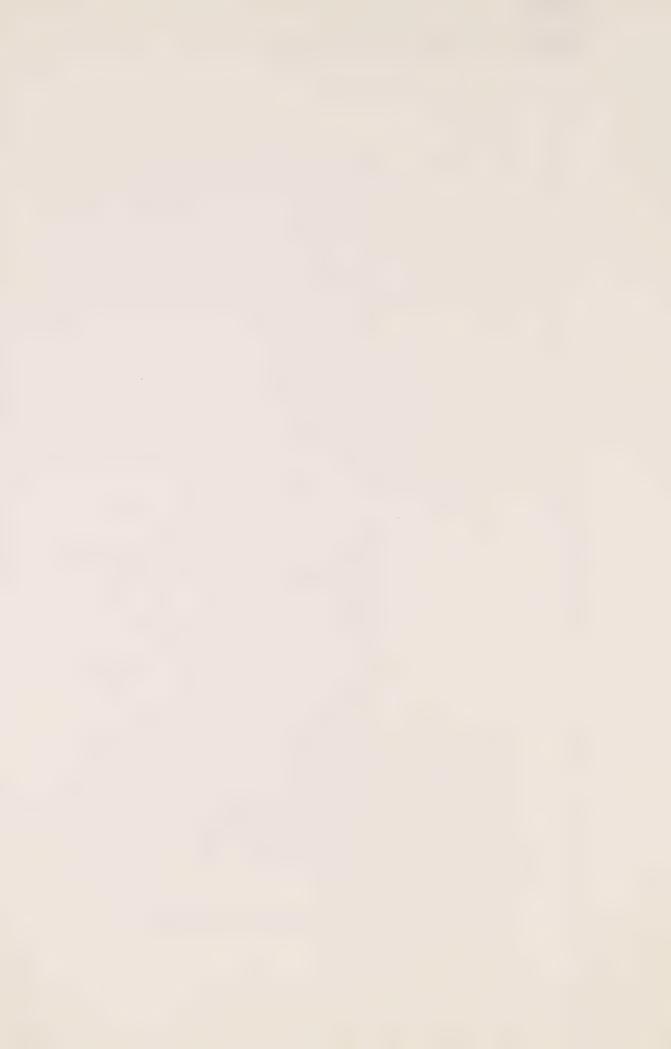
You are telling us, as I understand it, that that refers only to elimination of digoxin from the circulatory system?

A. That is correct.

- Q. And does not by any means indicate that digoxin which had been administered and which is bound to tissue is also being eliminated at that same pace, if at all?
- A. You are correct. That inference cannot be made."

Stopping there for a moment, Dr. Kauffman, do you agree with Dr. MacLeod's opinion that the rate of elimination of digoxin from tissue is not a matter that has been established with scientific certainty as the article suggests has been the case with the elimination from serum?

A. No, there certainly isn't as



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much, there is very little if any information looking at the rate of decline of concentration in heart muscle or in other tissues like there is available information looking at the rate of decline in serum.

Now, one of the problems if I have, if I understand what you have just read me, is that if he is saying that the drug can be eliminated from serum without being eliminated from the tissues, I can't quite agree with that because if you accept the pharmacokinetic principles of distribution and equillibrium, it is true that the drug leaves from the serum because it carries whatever is in the serum to the elimination organs. But if you accept the equillibrium phenomenon that I described earlier, then you have to accept that as it is eliminated from the serum compartment there is continual redistribution maintaining the ratio between the central compartment and the tissues so that as it is eliminated from serum it will be eliminated with a comparable half life from the tissues unless the whole concept of distribution and equillibrium is not correct.

Q. Well, Doctor, to be fair to
Dr. MacLeod, what he indicated from the passage that
I have read to you, amongst other matters, is that
digoxin bound in a variety of tissues in the body



Kauffman, dr.ex.
(Cronk)

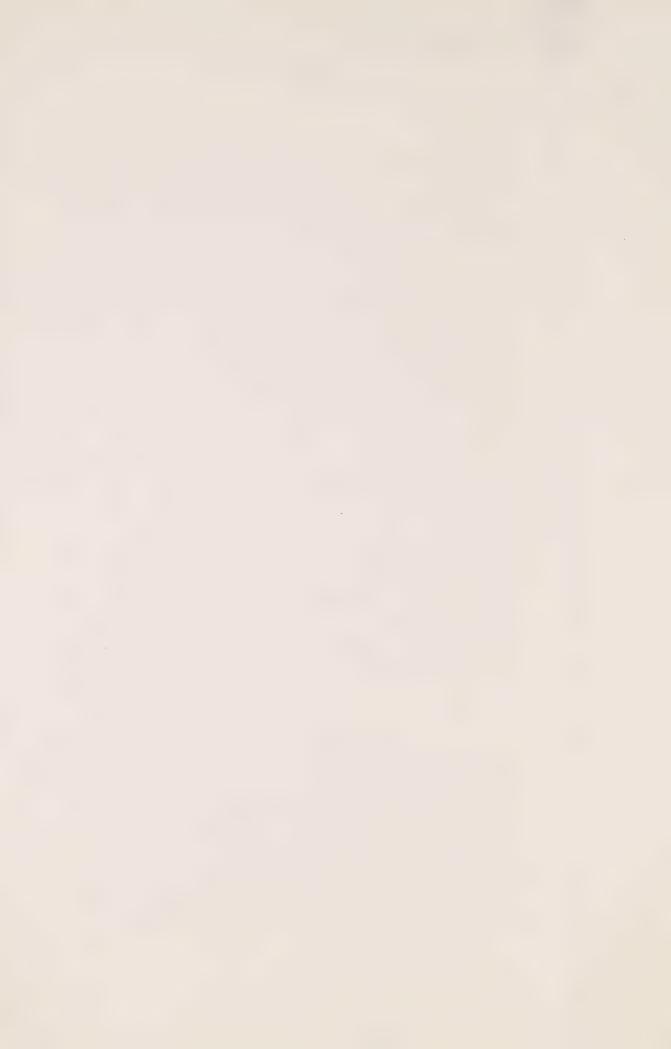
in his view will simply not be eliminated from those tissues within a predictable time frame. Do you agree or disagree with that?

are apparently different kinds of binding of digoxin.

A very very small amount of digoxin in tissue is specifically bound to the active receptor sites.

There probably is a great deal of the digoxin non-specifically bound in the tissue and even with the specific receptor site this binding is not irreversible it is a reversible binding, so that the amount of drug bound at any moment in time is related to the amount of drug there at any point in time. So that the individual molecules of drug can bind and unbind and the amount bound for a given concentration is related to the tightness with which it binds or the affinity that the particular binding site has for the drug.

So that as the concentration in serum changes the concentration in the central compartment will change, the concentration in the tissues will change and the binding will reverse. So, you can't say that the binding is irreversible and it will stay bound regardless of what is happening in the other compartments. In that sense I disagree with what you



just told me, if I understand what you sa	ić	E	
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Q. Well, Doctor, I take it that when you refer to non-specifically bound digoxin you are referring first to digoxin non-specifically bound to tissues. Do I have that correctly.

Q. All right. Is it also correct,

Doctor, that non-specifically bound digoxin is not

pharmacologically active in the body?

A. That is what is thought, yes.

Q. All right.

MR. SCOTT: I am sorry. I may have read it wrong but I thought Dr. MacLeod made precisely Dr. Kauffman's point. If my friend reads on that page and half way down the next page - now, I may have misread it and it may be for me to put it to him, but it might be convenient if my friend Miss Cronk agrees.

MS. CRONK: I have no difficulty.

The question beginning at 4274, Mr. Commissioner, from where I left off:

"Q. Therefore, let us take a child who is on a regimenof digoxin; if the last prescribed dose were a week before the time at which we take a level, we may find nothing in blood but that



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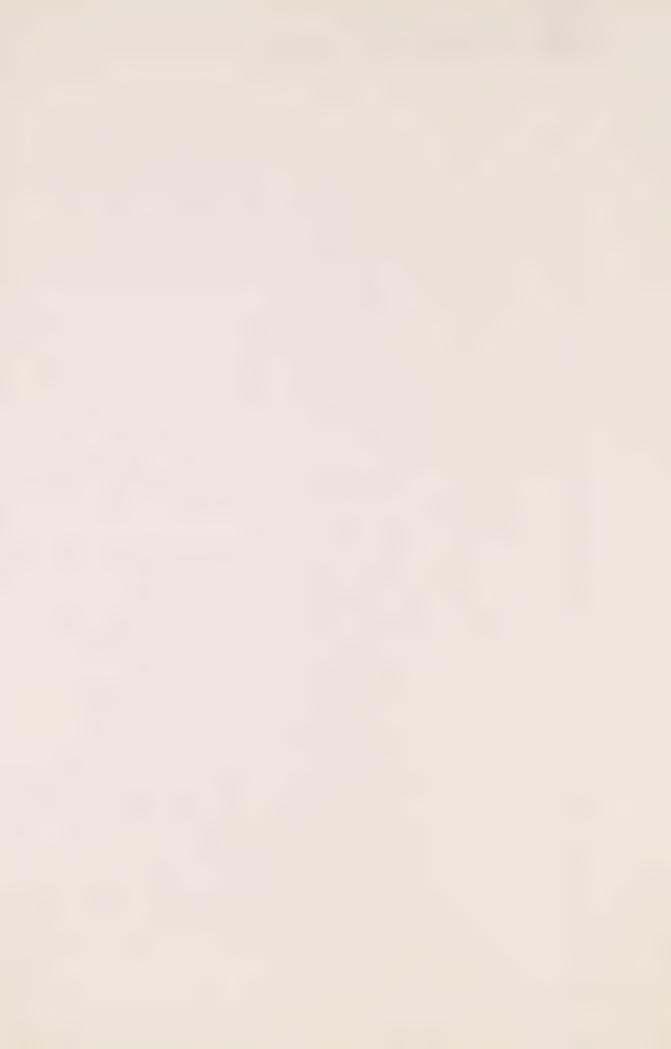
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"would not necessarily mean that there may not be still digoxin bound to tissue.

Would it be pharmacologically active still?

- A. I can't say that but your expectation would be that there would be digoxin remaining in tissue a week after the last dose of digoxin.
- Ω. And indeed for, I take it, a possibly very much longer period than a week?
- I think it is impossible to say what the actual duration would be under which the drug remained in the tissue. Clearly, there is some digoxin that is very tightly bound in tissues, to receptors. There is other digoxin which is rather loosely bound and, presumably, the loosely bound digoxin gradually comes out and appears in the urine. At some point, probably the tightly bound digoxin comes out too, but that might take weeks. Again, this is not something that has been studied,



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"although this paper gives us some hint of what is going on."

And then he continues to discuss the paper.

Doctor, do those further comments by Dr. MacLeod, and if they were relevant I apologize to my friend.

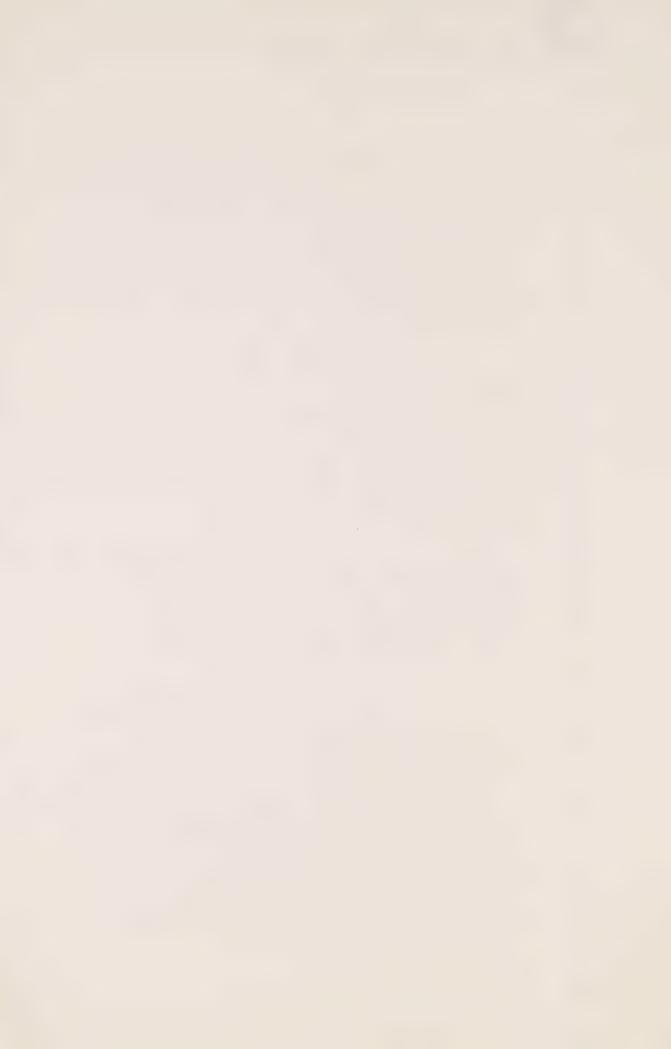
MR. SCOTT: Well, maybe they weren't but no one knows.

MS. CRONK: - assist you in your commenting upon whether or not the elimination factor with respect to digoxin from tissue is a matter that has been established in your mind?

Well, I don't think the rate of elimination from tissue has been established. I don't know what paper he is referring to here, so, I can't comment on that unless I see it.

> 0. Right.

But there is a study that was presented at the International Clinical Pharmacology meetings in Washington, D.C. in July of this year that I don't think is yet published as a full paper. What these investigators did was attempt to address this question in living children. What they did was look at, I believe it was 45 children who were on chronic digoxin therapy who



underwent cardiac surgery and at the time of surgery they obtained a piece of hard tissue and measured the amount of digoxin in it. In each of the patients that sample was taken at a different time after their last dose, I believe up to 20 days is the longest one if I remember correctly and I don't have that with me it is back in my hotel room but some of them as close as several hours, others as long as 20 days if my memory serves me correctly and scattered in between.

With that data they then attempted to pool those data and look at the rate at which digoxin appeared to decline in the heart muscle after the last dose. What they found was that the half life appeared to be 30 some hours; in other words, the half life from that study in hard tissue was essentially in the same range as what has been demonstrated in serum and that would be consistent with the understanding of equillibrium distribution of the drug in the body such that when it leaves the serum some replaces that from the central compartment, some replaces that from the loosely bound digoxin in the tissue, some from the tightly bound receptors and replace some of the unbound or loosely bound material. So, there is a chain reaction.

So that as the drug is leaving the body



from the serum there is a continual slow redistribution from the various areas where it is located.

Now, it is true that there could be digoxin in the tissue and you would be unable to measure it in the serum simply because your assay wasn't sensitive enough. I can't accept that there would be no digoxin in the serum and some in the tissue but I could accept that there could be some digoxin in the tissue and there would not be enough in the serum so that your assay could detect it if it was so low.

Q. I see.

A. In that sense I can agree with you but I can't agree that there could be none in the serum and still some in the tissue.

 $\Omega$ . Well, Doctor, did I understand you correctly to say that you had a copy of this paper in your hotel room?

A. It is an abstract and if it would be helpful I can bring it tomorrow or bring it at lunch or something.

 $\Omega_{\bullet}$  It would be very helpful. I would ask you to do that because I don't believe particulars of that paper have been previously produced.



## Kauffman, dr.ex. (Cronk)

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THE COMMISSIONER: Yes?

MR. STRATHY: Miss Forster tells me that we have it as an exhibit already, so, maybe we can check the exhibits.

MS. CRONK: Well, I will do that, sir and I thank my friend because if we have I am not familiar with it.

THE COMMISSIONER: That reminds me, we never did ask whether you got your baggage back from Air Canada?

THE WITNESS: Yes I did, thank you.

MR. SCOTT: Well, just so the Doctor won't have to have a pleasant dinner or watch television or anything if counsel might give him the Ochs paper if he hasn't seen that.

MS. CRONK: I would be glad to.

MR. SCOTT: Which is the one Dr.

MacLeod refers to.

MS. CRONK: I would be glad to.

THE COMMISSIONER: Mr. Strathy, you say this paper you think is one of our exhibits already?

MR. STRATHY: Well, that is what my colleague tells me, it is her recollection that it is in already.



THE COMMISSIONER: Does she remember which number?

MS. CRONK: The reason I thought it might not be, Mr. Strathy, is because ---

MR. STRATHY: She doesn't remember which number.

THE WITNESS: It is a short one-page abstract about this big.

MS. CRONK:  $\Omega$ . Of July of this year?

- A. Of '83.
- Q. Of '83.
- A. That is correct.
- Q. Thank you, Dr. Kauffman.

THE COMMISSIONER: Just to settle something very fundamental. When it leaves the tissue, does it go into the serum before it is excreted or not?

THE WITNESS: Let me tell you my way of looking at this.

THE COMMISSIONER: Yes.

THE WITNESS: As it leaves the cell it goes into extra cellular fluid. All the tissue contains some extra cellular fluid, fluid around the cells. From the extra cellular fluid it diffuses into the capillaries which then it is in the serum carried





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in the blood and then from there it either goes back into the extra cellular fluid in the tissues or is eliminated by the liver or the kidney.

THE COMMISSIONER: Can't get from the tissues out of the body without going through the blood at some time?

THE WITNESS: That is correct.

THE COMMISSIONER: Yes.

MS. CRONK: Q. Dr. MacLeod in the course of the same discussion with Mr. Lamek, Dr. Kauffman, was asked to direct his mind to the three children, three of the four children for whom digoxin was not known to have been prescribed. Specifically, his attention was then drawn to the case of Jesse Belanger, the child we have been discussing. This question was asked of him at page 4279:

> "I take it, Doctor, it is your view that a dose of digoxin any time in that 35-day period could still account for the finding of digoxin in the child's exhumed tissue?

Oh, yes. I think given the Α. uncertainties about the absolute concentration in those tissues, now, I wouldn't expect after 35 days to



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"find high concentrations but there certainly would be traces and there is no question that a method like gas chromotography/mass spectrometry would pick those up."



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"Q. And in the case of Baby
Lombardo who came to The Hospital
for Sick Children on the date of her
birth the administration could have
occurred at any time between
December 13th, the date of her birth
and her admission, until her death,
December 23rd, a period of ten days,
and I take it again administration
within that period in your view
would certainly account for the
exhumed tissue findings?"
"A. It would certainly give you

"Q. Right. Finally in the case of Baby Hines, unless digoxin were administered at North York General, again, one cannot rule out that possibility?"

a qualitatively positive test for

"A. No."

digoxin."

"Q. If digoxin were administered at The Hospital for Sick Children it could have been at any time between about 11:30, I believe we settled on



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hours of March 8th when he died, a period of just over two days?"
"A. Yes."
Now, stopping there, Dr. Kauffman,

the 5th of March, until the early

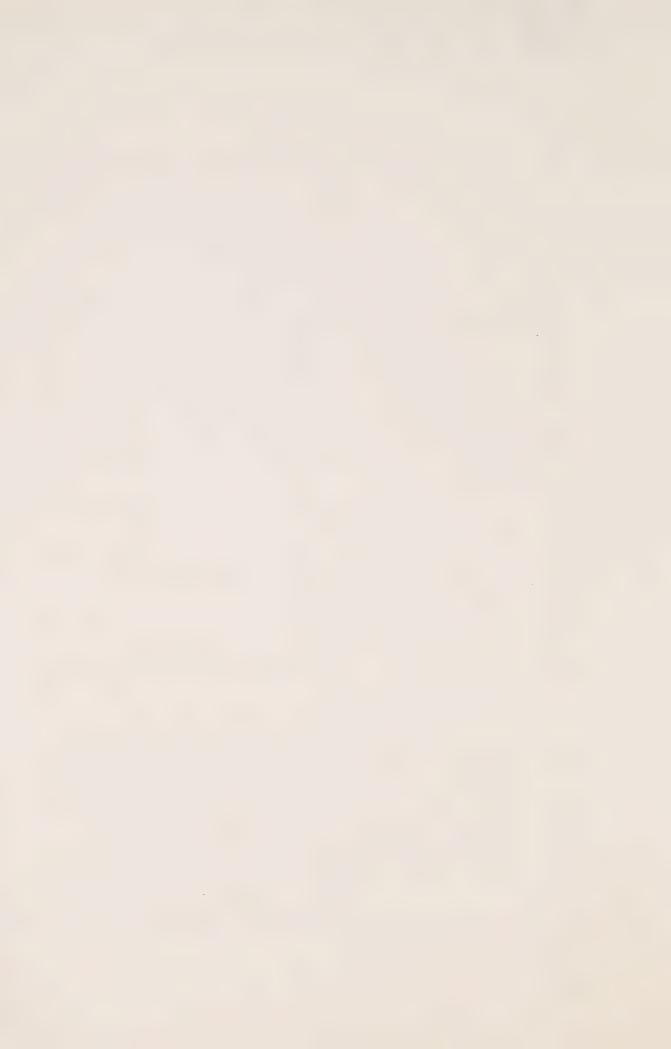
do you agree or disagree with the view expressed by Dr. MacLeod that a dose of digoxin administered in the case of Jesse Belanger at any point during the 35-day period of his hospitalization could account for the digoxin concentrations found in his exhumed tissues?

A. No, I don't think I fully agree with that. I would have to go, I would have to go into a fairly lengthy explanation but a simple answer to your question, I can't fully agree with that statement as you gave it to me.

THE COMMISSIONER: He is obviously not finished.

MR. SCOTT: My friend read the questions, which was the very thing to do, and then instead of asking after each question, do you agree with Dr. MacLeod's opinion, then rephrased the question in a different way.

Now all I read Dr. MacLeod saying is that you wouldn't find high concentrations but you



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might find traces that would --

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THE COMMISSIONER: The point I think is the time, I think that is where we started, this was whether or not you could still have traces so many days after the administration.

MR. SCOTT: Well all Dr. MacLeod said, as I read it, is there would be traces that would be picked up by these techniques.

Now it seems to me Dr. Kauffman may disagree with that and if he does he will want to say so, but the question that my friend phrased is quite different than that.

THE COMMISSIONER: All right. Well. MS. CRONK: May we take it in two stages, Mr. Commissioner, if it is of any assistance? THE COMMISSIONER: Very well.

MS. CRONK: Q. As my friend posits it, Dr. Kauffman, do you agree that digoxin administered any time during that 35-day period with Jesse Belanger could result in traces of digoxin in the exhumed tissues that were tested?

A. I suppose it is possible that there could be traces if you had a sensitive enough method to detect it. Can I use the paper to give you some perspective of why it bothers me?



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Absolutely, doctor, please do. Ω.

A. Because it really bothers me to go that far after 35 days. It is difficult to speak to this in any kind of a concrete way because we don't, we haven't defined the dose, in addition to not defining the time. So we have to make some kind of assumption on what kind of dose are we talking about. Are we talking about some excessive dose? Are we talking about one single maintenance dose? Are we talking about several maintenance doses or several loading doses? So we have a big problem that way.

Let us say we are talking about this baby by mistake getting somebody else's maintenance dose sometime during that period of his hospitalization; I think that is a fair assumption.

THE COMISSIONER: Well, it is fair, he either got somebody else's maintenance dose or got a special dose.

THE WITNESS: Or somebody gave him something he should not have had, yes.

THE COMMISSIONER: Yes.

THE WITNESS: We know it is one of

those two.

THE COMMISSIONER: It is certainly



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unlikely, although it may be correct on this, it is unlikely he got more than one dose when none was prescribed at all.

THE WITNESS: Anything is possible I suppose that he could have been given several intentional overdoses over the period of that few days, or could have been given a single overdose, or he could have been given several doses by error during that period of time, we just don't know.

MR. SCOTT: Can't we, leaving out the hypothesis that you suggested, which is a special dose, I take it --

THE COMMISSIONER: He wasn't suggesting it, I think it has been suggested by other people along the line.

MR. SCOTT: The suggestion on which you were acting.

THE COMMISSIONER: Yes.

MR. SCOTT: Leaving that out, I take it an accident could have produced either a maintenance dose or a loading dose?

THE COMMISSIONER: Yes, you mean an acute dose, an overdose.

MR. SCOTT: You have said, Mr. Commissioner, just as an observation, that we are not

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in this hypothesis going to deal with the possibility of two sequential accidents in respect of this baby.

THE COMMISSIONER: Yes.

MR. SCOTT: But if there was an accident, a single accident, it would be either a loading dose or a maintenance dose, are they not the two hypotheses that we have to deal with?

THE WITNESS: If we are talking about an error that is really your choice.

MR. SCOTT: Yes.

THE WITNESS: The other problem we have is we don't know whose — if it was an error we don't know whose dose it was and we don't know the size of that other patient X and we don't know how big the dose was. Let us assume he was on an infant cardiac ward, so the babies' weights range from 2.5 to 6 kilograms roughly. So let us say he got some baby's dose who weighed 6 kilograms, give it on the long side. Let us say he got a single maintenance dose that belonged to that other child. The usual maintenance dose is about 10 micrograms per kilogram. So let us say he got 60 micrograms as a single dose, by mistake.

Now Belanger weighed, I don't remember how much he weighed, can somebody help me?

MS. CRONK: Q. At the time of death, doctor, he weighed 3210 grams.



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A. So let's round it off to

3 kilograms. So for Belanger that would be -- for Belanger that would be 20 micrograms per kilo, okay.

Now, let's assume that it was given -he had no problems at the time and you wouldn't
necessarily expect him to have any symptoms from a
dose like this.

MR. STRATHY: I must be the slowest student in the class. If I may, Mr. Commissioner, how did you come to 20 micrograms per kilogram?

MR. SCOTT: Oh, come on, there is

always one.

THE WITNESS: 2 and 2 equals 4,

that is why.

MR. STRATHY: You had better go

back then.

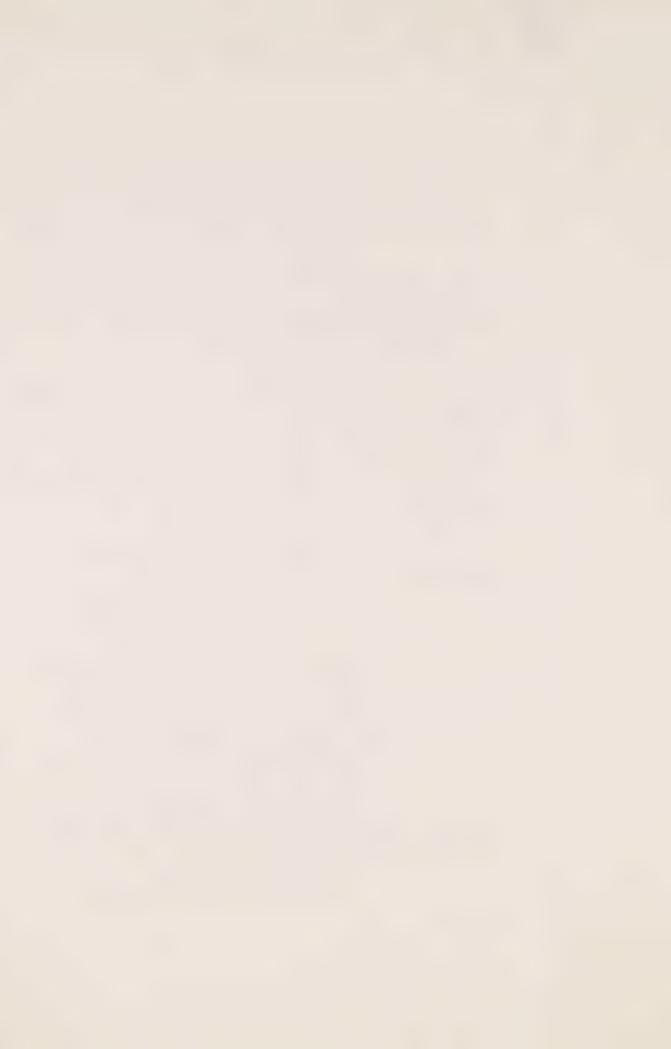
THE WITNESS: No. We are assuming that this child whose maintenance dose Belanger received by error weighed 6 kilograms.

MR. STRATHY: Right.

THE WITNESS: Belanger weighed 3 kilograms so his dose per kilo is twice the child who was supposed to receive the normal maintenance dose.

THE COMMISSIONER: Thank you. I am

with you.



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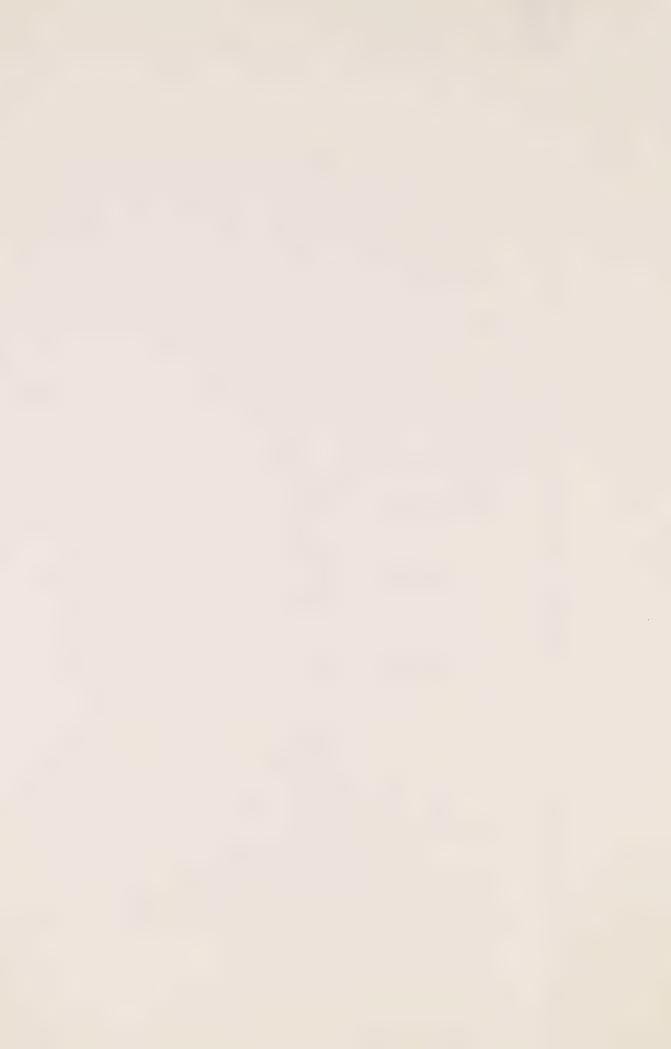
THE WITNESS: Okay. Now if we assume that he had no symptoms from this, it just happened, nobody discovered it, it went unnoticed and then he went on through his hospital course and died eventually from this catastrophic event that occurred on the 28th. So it was absorbed and it distributed. There was plenty of time for total distribution, wasn't there? Okay. So let us say the highest concentration was, in the serum, was into 10 litres per kilogram, with Belanger that would be 30 litres, wouldn't it, 10 times 3 is 30, so this distributed into 30 litres. Let us change this for -- so he got a total of micrograms. So his concentration is going to be 20 micrograms per 30 litres, and if you divide this you will get a .6, let us round it off to .7, total distribution .7 micrograms per litre, or .7 nanograms per ml.

Is everybody with me?
MR. SCOTT: Yes.

THE WITNESS: So the highest it could ever have been from that kind of accident would be a serum dig. level of .7.

Now, let us assume that in a baby

like this the ratio between the heart muscle and -
well what we have on him is skeletal muscle, we don't



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have heart I believe, I think it is skeletal muscle and liver. Okay, let us say that the ratio of skeletal muscle to serum in this baby, we can pick a number in a broad range, but let us say it is 20 to 1, so the concentration of skeletal muscle is 20 times this, that would be 14 nanograms per gram. The most it could ever have been, assuming no excretion or elimination at this point in time, within 12 hours after the accidental dose.

Now, if everybody can accept this

14, it could be 20, it could be 5, but with the

assumptions I am making in this ball park I think

you will see it doesn't make a whole lot of difference.

Let us take 14 nanograms per gram of tissue in his

muscle, the highest it could ever be with this kind

of accident.

Now, we have got to assume a half life. Again we have a big range to choose from. If you are willing to assume a midpoint in that range of 36 hours or 30 hours or 40 hours, I am not particular; let us use 40 hours it is a more even number. Let us say its half life is 40 hours, and if you will assume with me that the concentration in the tissue during elimination roughly declines with the same half life as the serum, then in 40 hours it is going



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hours it is going to be 1.7; in 160 hours it is going to be .8; and in 200 hours it is going to be .4 and on down until you can't measure it anymore. Now we are only out here at 200 hours that's around ten days at the most, and the assay methods are available — unless you use mass spectrometry are not going to project this. So if you use the GC/mass spec in tissue in these conditions you might detect a trace of this long under these — with this kind of an accident. At this, along about here you are not going to be able to detect any serum anymore because the concentration is going to be well below detectable limits within apparent half life, maybe it is there but you can't measure it with the usual assay methods.

So I could agree based on this kind of reasoning that you might see a trace as long as eight to ten days in tissue, but we don't see a trace in any of these things in these three babies, we don't see any trace, we see actual measurable levels that are detectable by HPLC and radioimmuno-assay.

MS. CRONK: Q. Now, doctor, as my friend Mr. Scott has suggested, if one were to postulate the other potential form of accident the



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child could have received a loading dose, not a maintenance dose, that is (a) a different feature; and secondly, to assist you further, the reading on the liver tissue from Jesse Belanger was in fact run by Mr. Cimbura we have heard on RIA/HPLC and mass spec.

Now, in those circumstances, doctor, how would your calculations change?

A. Well, a loading dose is usually 30 to 40 micrograms per kilogram. Let us say he got the loading dose for this other 6 kilogram patient; let's use the higher loading dose of 40 for the benefit of the doubt.



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So 40 times 6 would be 240 micrograms he would have received. And for him that would have been 80 micrograms per kilo which is a fairly large dose.

Now you don't get this loading dose all at once. It is routinely given as four divided doses and the first dose of the loading dose - over 24 hours - and the first dose of the loading dose is usually half of the total so he would have received 20 if we are assuming the single mistake theory, 20 times 6, which is 120 micrograms which becomes 40 micrograms per kilo for our patient. And times 3 kilos equals 120 micrograms total.

Now if you distribute that into total volume of distribution of 30 litres you come out with 40 nanograms per gram concentration if I have done my arithmetic right. But then you can take half of that is going to be gone in one half life; in five half lives 98% is going to be gone, and after that if you have a cubed block of cheese and you always take half of what is left you never will run out. So in that sense there could always be a trace there into eternity. But I don't think you could detect it after eight to ten days realistically.

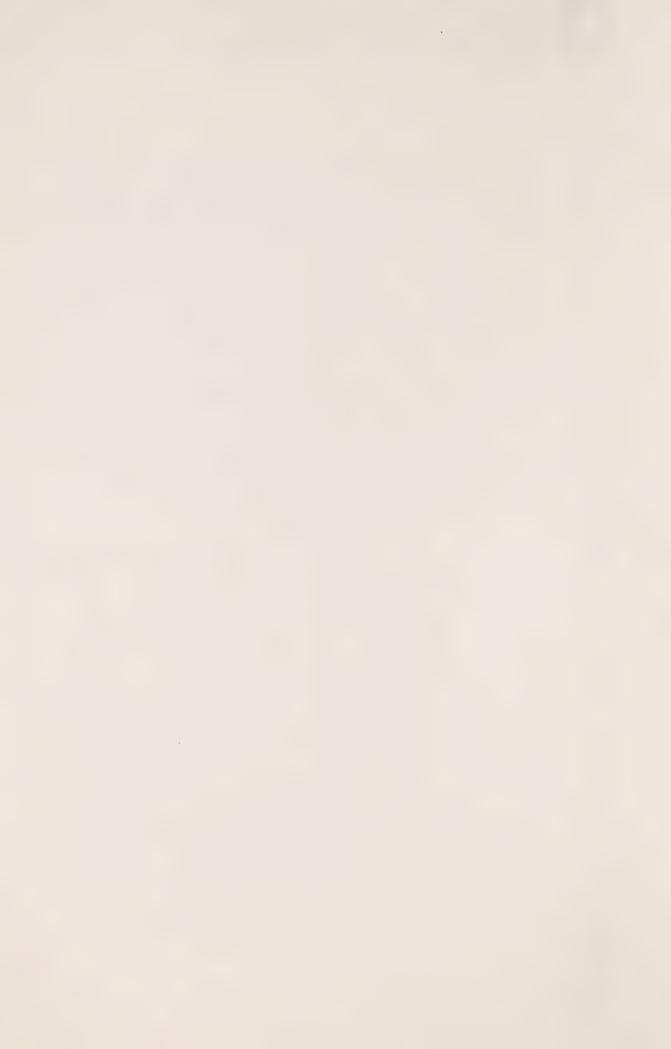
> $\Omega$ . Thank you, doctor. MR. SCOTT: I am told by my

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associate that is the same as the frog going across the pond. I have been absent so some of these analogies escape me.

MS. CRONK: I must say that one did too, and I was here, Mr. Scott, but there may well have been frogs but I didn't notice.

Q. Doctor, may we turn then if you would, please, to the case of Jordan Hines, and I assume, doctor, that we could in his case go through the same form of calculations that you just did on Jesse Belanger.

Once again, doctor, in respect of this child you concluded as stated in your reporting letter to Mr. Wiley that there was in your opinion a high probability that digoxin had contributed directly to his death. And once again I would ask you to explain for us the basis upon which you formed that opinion.

A. Well, this infant was two and a half weeks of age and was admitted with symptoms of apnea, bradycardia, listlessness, duskiness, poor feeding and an elevated temperature. And when I first looked at this medical record a year ago I said this baby must have been septic; he probably had group B streptococcal sepsis because this is exactly





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how that kind of baby would present at this stage. And I later found out that the cultures were negative so I couldn't substantiate that.

He apparently looked generally active and alert on admission but he continued to have brief episodes of apnea and bradycardia, and during those times he would look sick and somewhat lethargic and then he would perk up again when his heart rate was normal.

His ekg showed a sinus bradycardia, I quess this was on admission, with paroxysmal atrial tachycardia and a two to one block which means the upper chambers of his heart were beating twice as fast as the lower chambers and half the beats weren't being conducted to the lower chambers.

On the third hospital day he suddenly developed apnea, bradycardia, ventricular tachycardia, progressing to ventricular fibrillation. He could not be resuscitated, and at autopsy this child is different from the other two we just discussed because he had an anatomically normal heart and had no specific pathologic findings at gross autopsy.

He did have some non-specific findings which were suggestive of Sudden Infant Death



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Syndrome but I didn't place a lot of credence in that because the rest of his history and physical findings in the Hospital of course really didn't fit that at all, that syndrome at all.

Again, digoxin was never prescribed for this patient during his life and concentrations of digoxin were found in fixed heart tissue and exhumed liver and skeletal muscle, and as with the other samples of this nature it was impossible to put a quantitative interpretation on these.

They were helpful to establish that digoxin indeed had been received by this infant when it had never been prescribed.

The clinical history of this infant is consistent with sepsis, as I said, but his blood culture, his cerebral spinal fluid culture and his urine culture were all negative and didn't substantiate sepsis.

Now there is a real incidence of sepsis in infants this age whom we can never document a positive bacterial culture, so the absence of a positive culture doesn't absolutely rule out that he was septic, but it strongly mitigates against it.

The other thing that makes this a complex issue is that he had an inherent dysrrhythmia.



He had inherent abnormalities of his heart conduction and his heart beat and his heart rate, and if he did indeed receive digoxin this kind of abnormality could make him potentially more susceptible to toxic effects of digoxin than a child who didn't have this problem.

So that a concentration of digoxin which might not produce toxic symptoms in a normal infant could potentially produce toxic symptoms in an infant with this kind of rhythm disturbance.

The combination of his sudden death, the characteristics of his terminal episode and the fact that digoxin was present in tissues when it had never been prescribed led me to conclude that indeed digoxin could be responsible for this infant's death.

O. Those factors, doctor, in summary I take it are the same factors which led you to a similar conclusion in the case of Jesse Belanger? Once again we are talking about the timing of the child's death, the terminal event and the finding of digoxin in this case in exhumed and fixed tissues from the child?

- A. That is essentially correct.
- Q. Doctor, in the course of your





review of this case did you have access to or did you review the preliminary autopsy report that had been prepared on Jordan Hines?

A. Yes, I did.

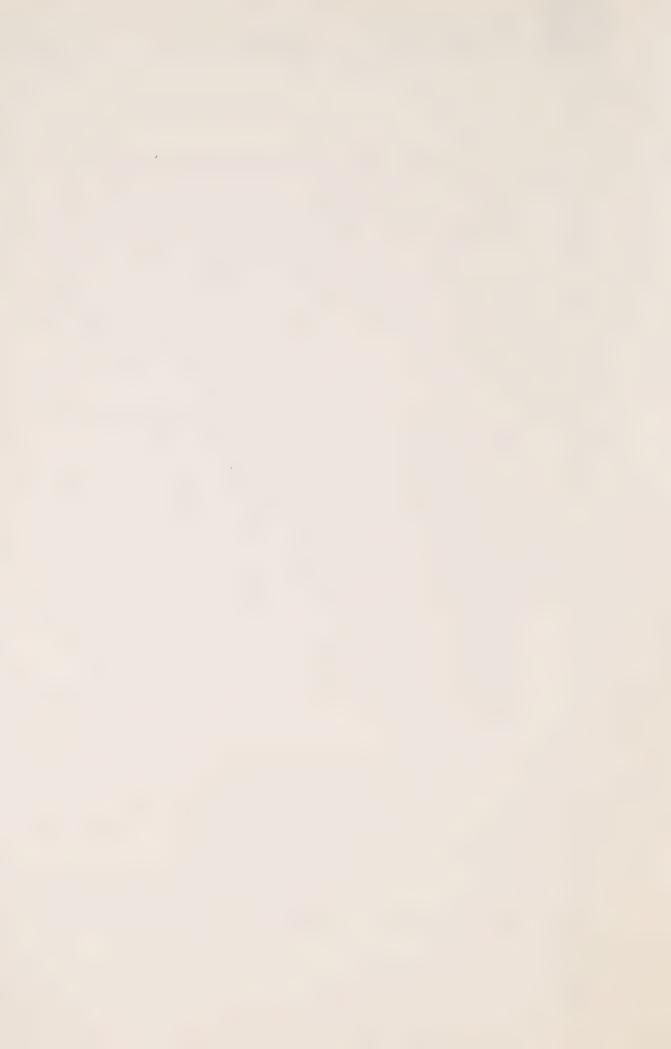
O. I would ask you to refer to that, if you would. It is in the medical record at page 29.

A. Yes.

Q. The last paragraph of the preliminary autopsy report at page 29, doctor, a number of pathology findings are outlined including congestion of the lungs and edema, fibrous thickening of the pulmonary arterioles suggesting chronic hypoxia, persistence of brown fat, gliosis in the brain stem in the brain, persistent extra-medullary hematopoiesis, the persistence of brown fat, the thickening of the pulmonary arterioles and then the pathologist who prepared this report indicates in the report:

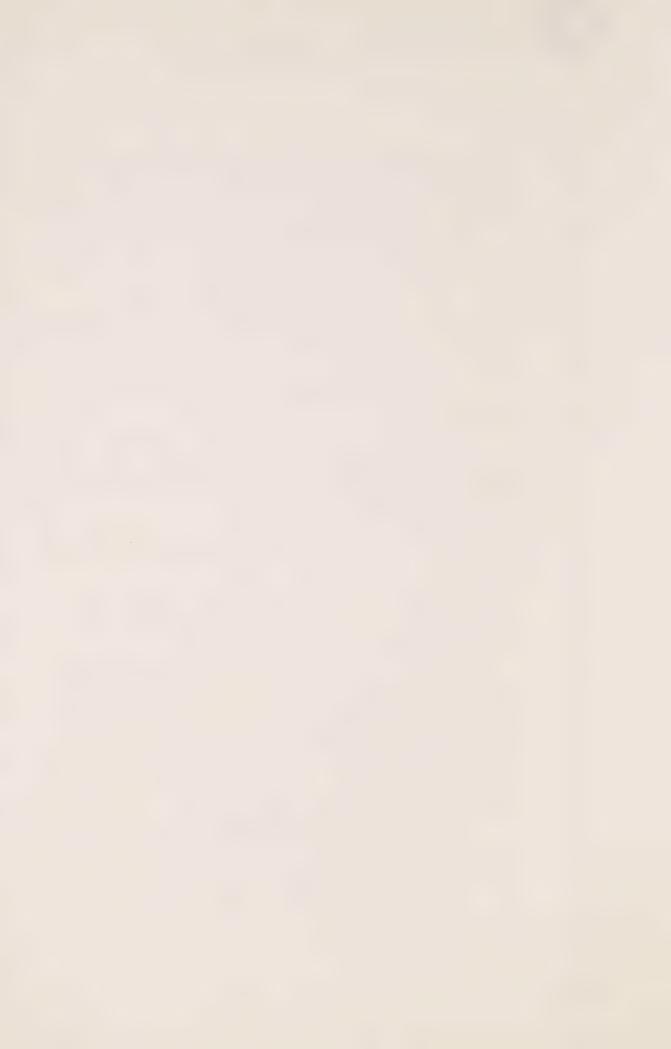
"This pathologic evidence, in conjunction with the clinical history, makes the diagnosis of a missed-SIDS a possibility."

I will tell you immediately, doctor, that Dr. Becker, the author of this report, has





1	
2	testified before the Commission and his evidence has
3	been that at conclusion of the autopsy he was of the
4	view that this child's death was indeed attributable
5	to missed-SIDS.
6	You have suggested, doctor
7	THE COMMISSIONER: Attributable to
	SIDS.
8	MS. CRONK: I thought it was to
9	missed-SIDS.
10	THE COMMISSIONER: Well, no, the
11	pathological evidence is missed-SIDS but the diagnos:
12	that he gave was surely SIDS.
13	MS. CRONK: I'm sorry. I had under
14	stood
	THE COMMISSIONER: Unless I have go
15	lost in the English language somewhere
16	MS. CRONK: I had understood, Mr.
17	Commissioner, and I am not sure much turns on this,
18	but Dr. Becker considered missed-SIDS to be a sub-
19	category, if you will, of SIDS, and my appreciation
20	of his evidence may be inaccurate.
21	THE COMMISSIONER: Right. You may
22	be right
23	MS. CRONK: But be it missed-SIDS
20	or SIDS



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THE COMMISSIONER: Whatever the medical profession wants to call it, missed-SIDS it is not because he died.

MS. CRONK: Well, sir, perhaps I could caution --

MR. SCOTT: I was told by the counsel that I was wrong about that.

THE COMMISSIONER: Well, everybody tells me I am wrong too, but it can't be missed. MR. SCOTT: Let's stick together on

this.

THE COMMISSIONER: What it is -surely the pathology is missed-SIDS because that takes 14 days to form, but surely the death is SIDS.

Now, I don't know. You can probably tell us better if it is so, but if the child died of missed-SIDS I have missed out on the language somewhere.

MS. CRONK: Well, sir, I can put it no higher than this: First, I do not think for the purpose of my intended question to Dr. Kauffman much turns on the matter; secondly, it was my understanding that that was what Dr. Becker had attested to, and I may be incorrect.

THE COMMISSIONER: Well, he did say



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something about that, yes.

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MS. CRONK: O. Doctor, in light of Dr. Becker's evidence, be it missed-SIDS or SIDS, it is clear I think and not in issue that in his view this child's death at the completion of the autopsy was explicable by the Sudden Infant Death Syndrome or some variation thereof.

You have indicated that in your view that syndrome was not consistent if I understood you correctly with what you observed in the clinical course of this child and the other findings that you observed in his record, and I would ask you why.

I think it is dangerous to Α. get hung up on the nomenclature for something we don't know what it is.

MR. SCOTT: We are lawyers, Dr. Kauffman, that is our specialty.

THE WITNESS: The SIDS I think is a clinical diagnosis. It is not a pathological diagnosis. It is a clinical diagnosis which may or may not be supported by pathological findings at death.

SIDS by definition is sudden infant death in an infant who appeared to be well up until the time he was suddenly and unexpectedly found dead for





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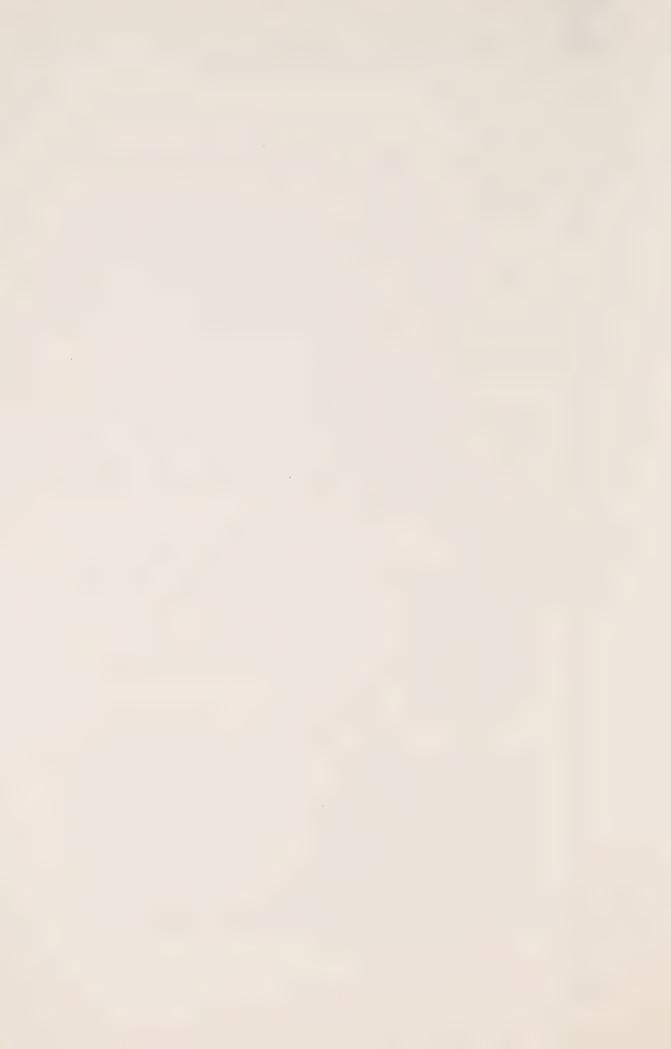
no apparent reason. Frequently there are no specific findings.

The findings reported in this report have been reported in infants who died unexpectedly and suddenly without any apparent cause and who were perceived to be in perfectly good health at the time they died.

As far as I am concerned if an infant has another illness or symptoms or physical findings which indicate that he is seriously ill, it by definition is not SIDS because there is another cause for the death.

So when this infant came in at two and a half weeks of age with rather profound symptomotology everybody recognized immediately that he was seriously ill. It could be a number of different things but there was no doubt that he was ill and having trouble.

So that along with the findings of abnormal heart rhythm, changes in heart rate and the other symptoms that he had, said that something was wrong with him, he is not a baby in normal health and the fact he died then must be related in some way to his previous illness, and as far as I am concerned cannot be defined as Sudden Infant Death



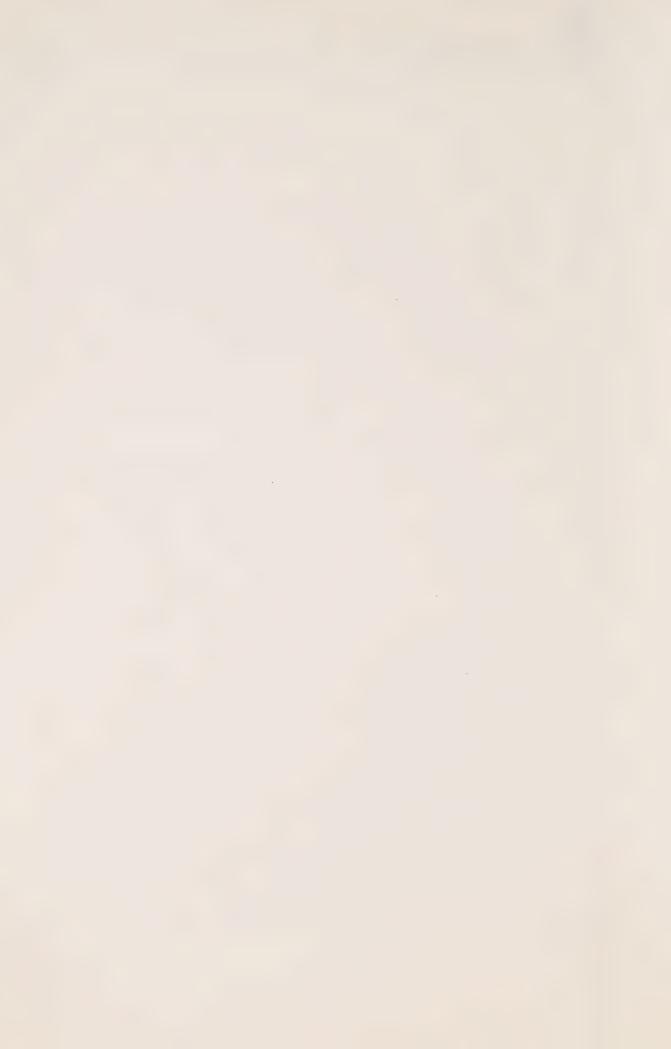
Syndrome.

Ω. Doctor, to make sure that I understand what you have said, are you saying that the fact of the child's illness on admission to Hospital was sufficient in your view to make a clinical diagnosis of Sudden Infant Death Syndrome inappropriate?

A. No, the fact that he had a pre-existing illness.

Q. Was there any other feature of his clinical condition or any other symptoms which he manifested during life which influenced you in reaching your conclusion in that regard?

specifically than I have without going through the chart again and refreshing my memory. But in general the answer to your question it was the fact that although he arrived and was having some arrhythmias, he did appear to be relatively stable and then had a sudden arrest with findings that were compatible with digoxin intoxication from which he could not be resuscitated. And then digoxin was unexpectedly found in his tissues when he had never received the drug. And that is a summary of the factors that influenced me.





17:

 $\Omega$ . And once again, doctor, we know that the concentrations that were found post mortem were in both exhumed tissues but as well in fixed tissues from this child.

Are the concentrations that were found in those samples indicative or confirmatory in your mind of anything other than the presence of digoxin in this child?



Kauffman, dr.ex.
(Cronk)

L BB/cr A. No, I think that they mean that digoxin was there.

as well from Dr. Speilberg in these proceedings, as you know, and specifically he has given evidence with respect to the range of frequency with which medication errors can occur in large sophisticated hospitals including teaching hospitals of the kind of the Hospital for Sick Children. His evidence in that regard has been - this is found, sir, at Volume 54, page 2134 - that approximately 10,000 to 15,000 doses of digoxin are given annually on the cardiology wards, Wards 4A/4B at the Hospital for Sick Children.

He said further, Dr. Kauffman, that the literature with which he is familiar suggests that in non-unit dose hospitals, including university or teaching hospitals, the range of frequency of medication errors, excluding wrong time errors, is anywhere from 5.5 per cent to nearly 20 per cent of all drugs being given. He also indicated that upon the introduction of a unit dose system that that range of frequency of errors fell to somewhere between 1 and 3 per cent but was reduced at least tenfold.

He said further, Dr. Kauffman, extrapolating from the literature, that there may be



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as many as 50 incorrect doses of digoxin given in any year to a child who is not prescribed digoxin.

That evidence is found, Mr. Commissioner, at Volume 55, page 2368.

Finally, Doctor, he has also testified with respect to the three children that we have just discussed: Stephanie Lombardo, Jordan Hines and Jesse Belanger that it is reasonably probable in his view that the three could have received digoxin in error.

Dr. MacLeod's view I tell you is slightly different. He has testified with respect to these three children, and this, sir, is found at Volume 64, page 4282 to 4283 that it is easier to say that perhaps one of them received a medication error and it is a little bit harder to say that perhaps two of them did and a little bit harder still to say that all three of them did. In short it becomes progressively less likely.

Accepting, Doctor, the possibility fully that medication errors do occur and accepting that each of these children may have received one or more doses of digoxin in error, in your view, knowing what you do about these cases, is it likely that all three of them received digoxin by accident



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or is it something about which you can't at all express an opinion?

Well, I certainly agree that medication errors unfortunately occur. Fortunately the majority of them do not result in increased morbidity or mortality for the patients. Unfortunately a few of them do.

When one tries to estimate the probability of a medication error occurring in this particular situation I think you have to look at several things. We certainly have to consider this as a possibility and try to decide what the probability is, that it could have happened.

I agree that the probability of this kind of error occurring and causing the digoxin to be present, whether or not it was causally related to their death, the probability declines with increasing numbers of this happening to increasing numbers of individuals, especially over a relatively short time, several months.

It becomes even more improbable in my mind when you see that it tended to be clustered if we are talking about these patients - it tended to be clustered in one area of the Hospital and at one time of the 24-hour period.



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If you were talking about occurrence of random errors being made, it should occur with equal frequency throughout the Hospital and throughout the time and I wouldn't expect to see this kind of clustering if it was a random error.

So, if you do accept the hypothesis that all of these resulted in medication errors then you have to say that there was something unique about this particular ward and this particular shift that increased the probability of a medication error occurring and the probability of that happening is I think quite small.

So, I find it hard to postulate medication errors to explain all of these cases, particularly - well, we are talking about four right now, your question related to the four cases, is that correct?

- Q. That is correct.
- A. So, I find it difficult to accept as the most likely hypothesis a medication error to explain the findings in these four patients.
- Q. Doctor, the possibility of repetitive medication error was a matter, as I understand it, which you did specifically consider at the time that you were delivering your first



## ANGUS, STONEHOUSE & CO. LTD. Kauffman, dr.ex.

then.

reporting letter to Mr. Wiley?

- A. Yes, I did.
- Ω. And you considered it specifically with respect to these four children?
  - A. Yes, I did.
- Q. And if we turn to page 12 of your report, Doctor, under your Miscellaneous Comments section, the last two sentences of that paragraph in substance record the opinion that you have just now expressed?
  - A. That is correct.
- Q. I'm sorry, sir, page 12 of the first reporting letter.

Mr. Commissioner, I am about to turn to the case of Allana Miller. Would this be an appropriate time.

THE COMMISSIONER: Yes, until 2:30,

MS. CRONK: Thank you, sir.

Sir, it may be of some assistance to counsel and yourself if I raised this matter now.

I have some concerns about the possibility of completing Dr. Kauffman's evidence by the end of the day on Thursday of this week. He is aware of it and I have asked him whether or not it is at all



possible were it to be necessary that he be available on Friday, subject of course to your own views and the convenience of other counsel.

He has agreed to at least check with his offices over the noon hour and find out whether that is possible. The difficulty of course arises because were it necessary to bring Dr. Kauffman back we have other out-of-town witnesses scheduled for the interval between now and Christmas and indeed Dr. Kauffman's own schedule makes that virtually prohibitive.

So, I raise it only now in case other counsel wish to address any submissions to you.

THE COMMISSIONER: Do you think you will be through with your examination by tonight?

MS. CRONK: I'm going to try, sir, but it is possible that I will not be.

THE COMMISSIONER: Yes. Well, you can tell us at 4:30 or whenever.

MS. CRONK: I will, sir.

THE COMMISSIONER: Or 5 o'clock. Yes,

Mr. Shinehoft?

MR. SHINEHOFT: Well, Mr. Commissioner, there is another possibility as opposed to coming back on Friday which I find myself is somewhat



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inconvenient and that is to stay late until 6, 7, 8 o'clock at night.

THE COMMISSIONER: Well, I agree that that is another possibility and you being young and vigorous have no trouble but with those of us who are a little older and perhaps with the witness it becomes, if we sit past 5 o'clock, I am not too sure how productive it is, that's the problem.

I would prefer to sit on Friday rather than sitting until 7 or 8 at night, that's all, on the other days. But we can fit in your cross-examination as we have in the past if you can't be here on Friday and if Dr. Kauffman can. But we will just wait and see what happens and you will perhaps know for us, will you, by this afternoon?

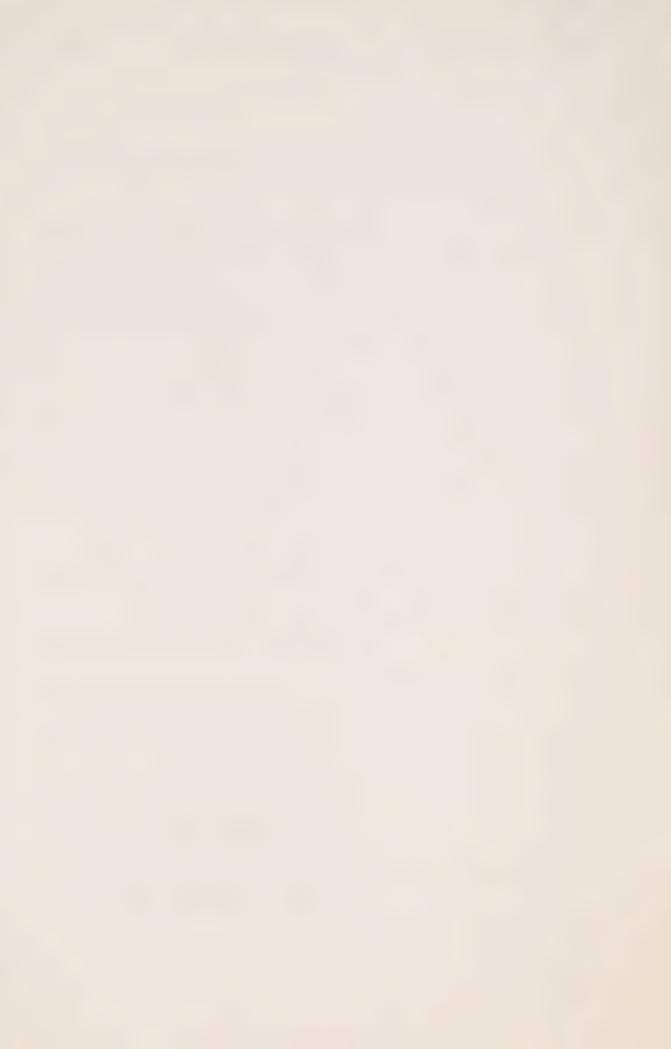
THE WITNESS: I will call today and check my calendar.

THE COMMISSIONER: Well, you will certainly know by tomorrow and we have now all been warned that Friday is a possibility.

THE WITNESS: Yes.

THE COMMISSIONER: But perhaps if we all got snappy we might even finish by Thursday.

MS. CRONK: I feel the eyes and the suggestions, sir.



THE COMMISSIONER: Yes, all right.

Until 2:30 then.

---Luncheon recess.



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-- on resuming.

COMMISSIONER: Yes, Mr. Lamek.

MR. LAMEK: Mr. Commissioner, Miss

Cronk has kindly agreed that I may say something now with respect to a question that arose yesterday, and that was about the production of the Minutes of a meeting held on August 27, 1982 at the Police Headquarters, which Dr. Kauffman was the first meeting which he attended after his retainer as a consultant.

As I said yesterday, sir, it has seemed to me that portions of those Minutes were indeed relevant and admissible, relevant to Phase I of the Inquiry, and that is to say, "Cause of Death".

I extracted those portions of the Minutes which in my view should be produced, and I have had those portions duplicated, sir, and they have been distributed to counsel.

I have spoken to Mr. Young about the production of these portions of the Minutes of that meeting, not I stress to obtain his blessing or approval, but merely to advise him of what I proposed to do so that he might consider what position he might want to take when I tender these Minutes as an exhibit.

He has told me that he has no objection although he would like to address you, sir, in a couple of minutes.

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Perhaps I should explain the nature of the portions of the Minutes that I have excluded from the document that I am going to be offering, sir.

The meeting generally served as a general update of the continuing police investigation, and this of course was some four or five months after the end of the Nelles preliminary inquiry. And consonant with your recent ruling as to the scope of Phase II, I have taken the position in editing these Minutes that the matters pertaining to the police investigation after the discharge of Nurse Nelles will not be tendered in evidence unless they are relevant to matters in Phase I and/or Phase II as defined by you, sir.

I have thus deleted from the original Minutes references to matters such as the organization, storage and retrieval of information gathered in the course of the investigation:

The shifting focus of the investigation following the discharge of Nurse Nelles.

An epidemiological study which was then contemplated but which was not in fact undertaken.

The proposed contacts with parents of children who had died on 4A and 4B, that was one of the topics that was discussed at this meeting and



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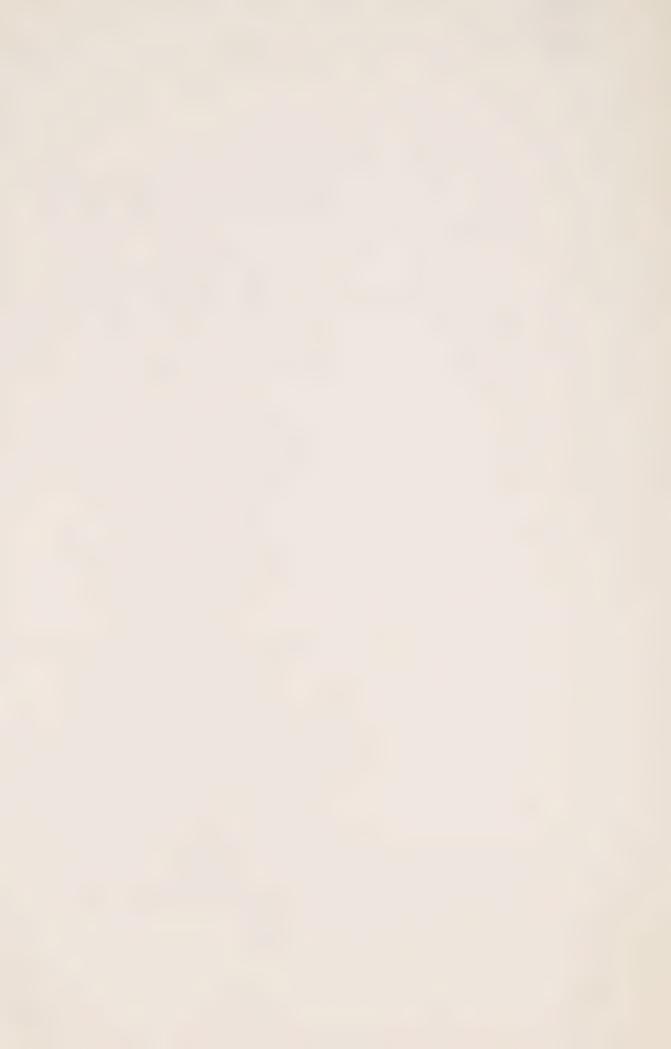
of course was the subject matter of the later meeting on September 13th, of which we have already seen the Minutes.

I have deleted too references to certain children's deaths were then being considered but who did not die on Ward 4A and 4B in our time period and therefore were not within your terms of reference, sir.

I have deleted references to further exhumations which were being suggested at the time, although I have left in the Minutes Mr. Cimbura's views as to the utility of those things because it seems to me that those views go to the question of the interpretation of the levels found in exhumed tissue.

I have deleted references to ongoing interviews of Hospital staff, and I tell you, sir, and through you, all counsel, that those references did not in any event contain any mention of the substance of those interviews or any information flowing from them.

Finally, I have deleted references in these Minutes to the then threatened civil action by Nurse Nelles and to certain civil actions which had been instituted by parents.



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In short, sir, I have made what I hope is my best effort to identify and include those portions of the Minutes that are relevant to the scope of this Inquiry as you have defined it, and I offer you, sir, the extract from the Minutes of the meeting of August 27, 1982 as the next exhibit.

THE COMMISSIONER: Yes.

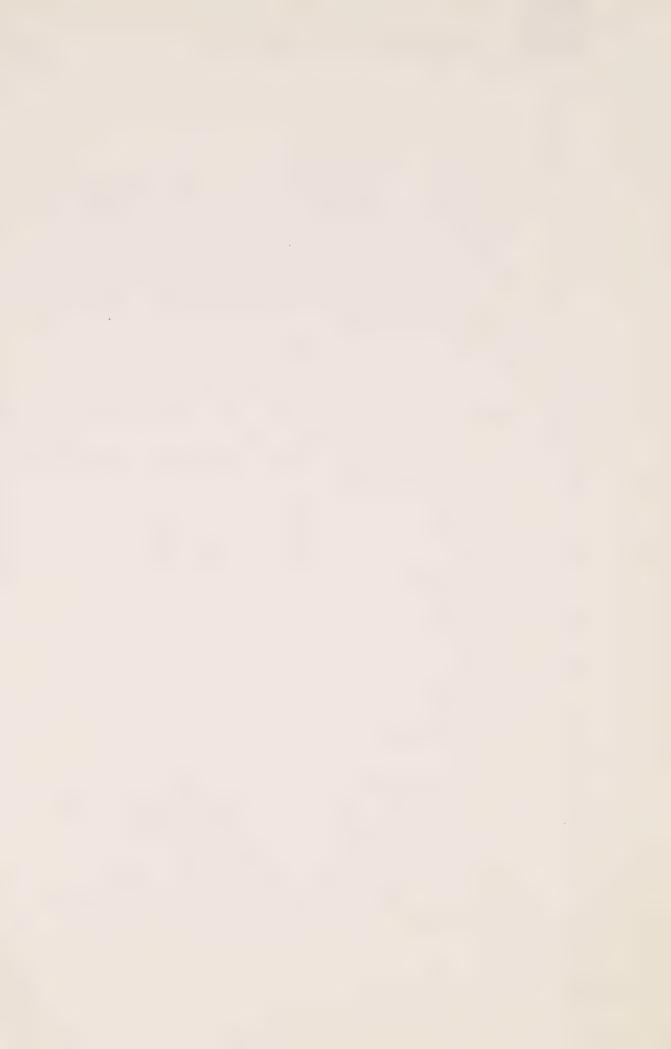
Mr. Young, have you any comments on this going in?

MR. YOUNG: I wonder if I might make a very brief statement.

THE COMMISSIONER: Yes.

MR. YOUNG: As Mr. Lamek told us, he approached me this morning and informed me that he intended to produce an expurgated version of these Minutes. I should state just so the record is clear it was Mr. Lamek and Mr. Lamek's office who expurgated these Minutes, not our office or the Police Department.

Pursuant to your recent judgment,
Mr. Commissioner, that this Inquiry should be confined
to consideration of the police investigation up to
and not beyond May 21, 1982, the date that Susan
Nelles was discharged, our position has consistently
been that the bulk of the notes taken at meetings



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involving police officers do not deal with the cause of death and would not assist this Inquiry in trying to determine the cause of death.

We have also stated on numerous occasions that if Mr. Lamek or you, Mr. Commissioner, approached us and suggested that portions of these Minutes or these notes should be introduced because they were relevant, we would consider not raising any objection to the introduction of these Minutes. We didn't object when the September 13th Minutes were tendered and we are not objecting today to the introduction of these other notes.

However, I would observe, Mr.

Commissioner, that this latest set of Minutes were
made during the second police investigation, and I
think they require just a little bit of explanation.

For instance, the notes were taken by an available secretary at the Police Headquarters. She had no familiarity with the technical terminology being used, with medicine, science or the ongoing investigation, and as a result, and as I will point in a few moments, Mr. Commissioner, there are a number of typographical and other errors.

In addition, I should also make clear that this is not a verbatim transcript of what



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and "metres"?

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went on there. They are not really Minutes of the meeting either; they are simply her notes that she typed up and they were not accepted at any later meetings.

I think, Mr. Commissioner, I can accurately say they were simply maintained as matter of internal record for the Police Department.

As I referred to a number of errors a moment ago, Mr. Commissioner, I point out that there are a number of references to "grams" and I think on other occasions too to "metres", and I think what the young lady meant was "nanograms", I think that will be clear --

THE COMMISSIONER: I'm sorry, "grams"

MR. YOUNG: "Grams" and "metres", "491 grams" and I think it really should read "nanograms", I'm sorry.

THE COMMISSIONER: What do the "metres" equal?

MR. LAMEK: Page 3, for example, Mr. Commissioner, you see references to --

THE COMMISSIONER: Once again a copy has gone to everybody but me.

MR. LAMEK: I'm sorry, you wouldn't



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accept it from me. I would be delighted to give you one, sir.

This is by way of example, on page 3 there are references in the middle paragraph to "the heart concentrations ranged between 201-296 m. per gm.", which I take to be the abbreviation for "metres per gram".

MR. YOUNG: I would strongly suspect, Mr. Commissioner, that she really meant to say and what was said was "nanograms".

MR. LAMEK: I think that to be a fair inference.

MR. YOUNG: And you will note on the second page in the fifth paragraph there is a reference to "gram" and once again that really doesn't make a whole lot of sense. I don't expect that is really what was said at the meeting.

There are a few other examples of that, minor errors, Mr. Commissioner, on the second page, the eighth paragraph, the last word in the fourth line is listed there as "miocardian", and I expect that is "myocardium".

THE COMMISSIONER: This young lady didn't have a six-month course the way we have.

MR. YOUNG: That is right. I recall



having trouble with these same terms.

On the fourth page, the second paragraph, the second line, the second word, Mr. Commissioner, is a reference to "Bruce Loran" and once again, I suspect that is "Bruce Floryn".

The same paragraph in the fourth line, the third-last word on that line, "Packgun". Once again, Mr. Commissioner, I think it is pretty clear that is not what was said. It is likely "Pacsai".

THE COMMISSIONER: Yes.

MR. YOUNG: And the last typographical or error of some sort, Mr. Commissioner, is contained on the same page, the last paragraph, the third line, there is a reference to "HRP", and I believe that should be "HPLC".

Mr. Commissioner, other than those comments we have no objection to these being tendered and accepted as an exhibit.

THE COMMISSIONER: Then the Minutes, the expurgated Minutes of the meeting of August 27th will be Exhibit 269.

--- EXHIBIT NO. 269: Expurgated Minutes of meeting of August 27, 1982.

MS. CRONK: I'm sorry, sir, what was

the number?





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THE COMMISSIONER: 269.

Yes.

MR. LAMEK: Mr. Commissioner, I have a further document to tender as an exhibit. Dr. Kauffman, as you know, was initially retained as a consultant to the Police and to the Crown Attorney's office. He also acted as consultant in Clinical Pharmocology to the team from the Centre for Disease Control and the Ontario Ministry of Health, the authors of the Atlanta Report.

As you know, an expurgated version of the Atlanta Report was distributed to all counsel some time ago for whatever assistance it might be to them in the cross-examination of other witnesses.

Now for the first time of course we have a witness in the box who was a contributor to the Atlanta Report, and it has occurred to us that it may be helpful, counsel may find it helpful to refer in cross-examination to that report. If there is to be such a reference it is my view it might be appropriate that the report be in evidence.





BB EMT/cr

I am therefore offering now, sir, as the next exhibit a copy of the expurgated version of the Atlanta Report.

THE COMMISSIONER: Yes. All right.

MR. LAMEK: Oh yes, just one point:

appended to it, sir, is a key of the code for the

various children by number and name. On the very

last page the names are supplied that correspond

with the numbers of the children in the categories

A,B and C.

The last child named in Group B, number 02019 is identified as Friesen. Indeed that child should be Gage, not Friesen. For "Friesen" read "Gage" on that final page.

THE COMMISSIONER: All right. Exhibit 270.

THE COMMISSIONER: This is the same document that was distributed I take it. It is not changed in any way from the ---

MR. LAMEK: It is the document distributed earlier to counsel. All counsel.

THE COMMISSIONER: Yes. Thank you,

Mr. Lamek.

The only other thing I want to say,





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and Dr. Kauffman is not enthusiastic about it but is prepared to be here if necessary on Friday, and I think we have to accept his offer because it would be almost impossible to fit him in at any other time if it is necessary. I am still hopeful that we will be able to finish and he is perhaps even more hopeful than I am that we will be able to finish by Thursday night, but if we have to go over to Friday we will.

MR. STRATHY: Just while you are talking about scheduling, Mr. Commissioner, I have a problem tomorrow morning and possibly all the balance of the day tomorrow. I am simply going to ask if I may to take my turn on Thursday rather than tomorrow.

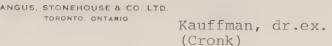
THE COMMISSIONER: Yes. Yes. I don't think there will be any real problem with that.

There is one other thing I should mention too and that is on Monday morning the Council of Judges is meeting - is meeting I think all day but for some judges I guess a half a day is as much as they can expect. It is all I am going to take so we won't start until 2:30 on Monday.

All right, Miss Cronk.

MS. CRONK: Thank you.

Q. Dr. Kauffman, I would ask you to turn now if you would, please, to the case of





Allana Miller.

Your summary and analysis with respect to this child commences at page 5 of your first reporting letter to Mr. Wiley. Do I have it correctly, Dr. Kauffman, in this case as well you have expressed the view in your written reports to Mr. Wiley that it is probable that digoxin contributed directly to this child's death?

- A. Yes, that is correct.
- $\Omega$ . Once again, Doctor, could you help us, please, as to the basis upon which you formed that opinion?

A. This infant was 11 months old when she was admitted at this time. She had had long-standing congenital heart disease becoming symptomatic, as I recall, some time around the fifth or sixth month of life. Had been treated for some months with digoxin as well as diuretics and then was admitted because of progressive congestive heart failure at this time. She was in the Hospital approximately 48 hours or maybe a little less prior to her death.

During her hospitalization she had documented bradycardiac episode. She had repeatedly documented irregular heart beat, and was suspected on admission of possibly suffering from digoxin



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intoxication. However, a digoxin level obtained on the date of admission was reported as 0.6 nanograms per mil. on the record I looked at.

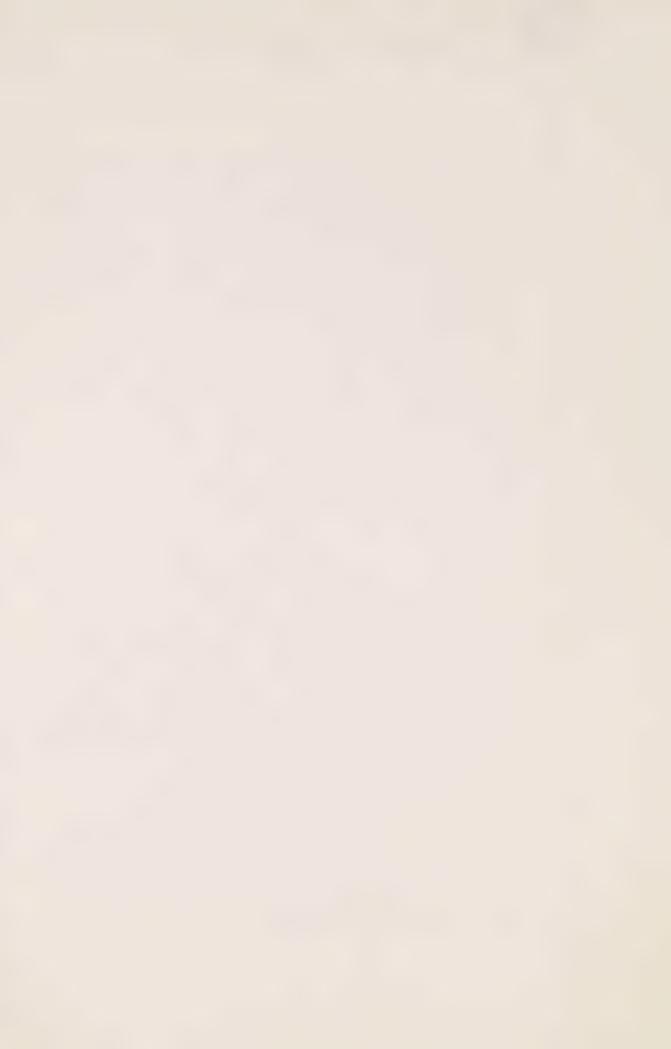
She seemed to be getting progressively more symptomatic from her congestive failure with difficulty breathing.

The evening prior to her death did tolerate several feedings. Because of her slowing heart rate periodically and her irregular rhythm her digoxin dose was held I think after the 20th, the date prior to her death, and so she did not have any digoxin prescribed from some time on the 20th until her death early morning of the 21st of March.

She also had some other laboratory studies done, and I didn't look at the laboratory sheet in the record. I have a copy here of the latter several days. I have laboratory reports from Allana Miller with dates of 14 October, 15 October, 21 October and 22 October and I am confused because I think the date of her death was 21 ---

> That is correct. 0.

- and I don't understand a laboratory report dated the 22nd at time 10:00 a.m., so I will have to refer to the chart to clarify that unless you can help me.



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2	Q. The chart, Doctor, is Exhibit
3	115, and the biochemistry reports appear in a - it
4	is two pages starting at page 69 and there are
5	further - I am sorry, Doctor, the earlier reports are
	found at pages 87 and 88.
6	A. Okay. I see on page 86 the
7	first copy that looks like my copy.
8	Q. Those are from October of
9	1980, Doctor.
10	A. Right. Those are from an
11	earlier
	Q. Admission.
12	A earlier hospitalization.
13	Q. Starting from page 87 you
14	will see readings commencing on March 19 through to
15	March 20 and then there are others in the record
16	for March 21st.
17	A. Okay.
18	Q. Does that assist you, Doctor?
19	A. Yes. What I wanted to point
	out was that on admission on the 19th of March her
20	blood gases appeared to be essentially normal. He
21	pH was 7.32. Her PCO <sub>2</sub> was 47 and the PO <sub>2</sub> was not
22	recorded but she has a normal bicarbonate. But those
23	look normal. Her electrolytes including her potassium



are all normal and her BUN was 19 which is approaching the high side of normal range.

The digoxin concentration in serum reported on that day was 0.6. That is the one I just referred to.

Then if we move to the next day at 1430 on 20 March we can see that again her sodium potassium and chloride are essentially unchanged. They are all normal. Her potassium was 3.8.

Her BUN the following day is 10 which is still within the normal range, and in addition to that the creatinine is 0.5 which is another measurement of the kidney function so we see that her kidney function on the 20th day prior to her death according to the data on the laboratory report is normal.

Then I don't think there is any additional laboratory report following 1430 on 20 March.

Q. Will you turn, Doctor, to page 69 if you would and you will see the results from various tests on the 21st of March.

A. Okay. Thank you.

Now as I understand it this sample was drawn after the death; is that correct?



referring to?

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0. Which page are you now

A. I am on page 69, 21 March.

0. There is no time indication there, Doctor, but to help you it is clear that the digoxin specimen reported on the next page was drawn after the death of the child.

THE COMMISSIONER: The destination pathology ---

MS. CRONK: I am sorry, sir, I didn't hear you.

THE COMMISSIONER: The destination is Wouldn't that help us? pathology.

MS. CRONK: Yes, it may well be that this sample as well was drawn after death.

THE WITNESS: There is no time or designation. This becomes - it is an important question to me because the potassium is quite high. If that is a post mortem sample it has no particular relevance; if it is an ante mortem sample then it does.

MS. CRONK: O. As the Commissioner suggested we have heard evidence from certain of the biochemists from the Hospital for Sick Children that when these forms indicate in the top right hand corner



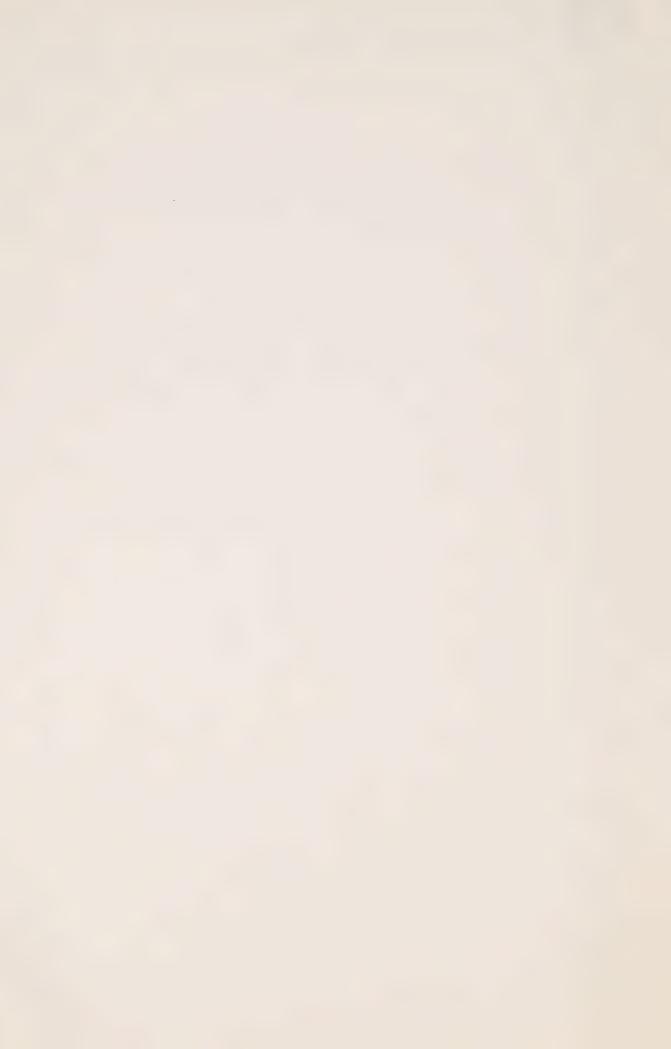


of the page the destination for pathology, that has been in the cases we have examined referrable to specimens taken after death.

A. I will assume that this is a post mortem sample then.

So the potassium of 9 reported on 21 March is of no particular significance to me.

What I want to point out, though, is based on laboratory data this child had normal renal function and had normal blood gases at the times they were measured during her short hospitalization.





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In addition, I think that the digoxin concentration measured on the 19th of 0.6 nanograms per millilitre was consistent with the maintenance dose that she has been on during the previous months. Then at approximately 1:45 a.m. on 21 March she suddenly developed, became more bradycardic, developed an irregular heart rate and is described as beginning to gag and vomit along with those symptoms. Around that time she also had a generalized seizure. Her bradycardia progressed to cardiac arrest and resuscitation efforts were not successful.

Then, as we just noticed, the serum concentration obtained approximately six hours after her death was measured at the Hospital as 78 nanograms per millilitre. Another post mortem sample that I think was done at CFS was 69 nanograms per millilitre. Subsequently, the only tissue concentrations that were available were on preserved tissues. There were no fresh data available in this patient and digoxin concentrations in the myocardium from tissues preserved in Klotz solution were reported as somewhere around 5 to 7 nanograms per gram of tissue, it was very low.

So, the combination of a child who, on admission, was shown to have a digoxin concentration



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compatible with her maintenance dose of 6.0 and had no additional doses administered after the day prior to her death had normal renal function as near as I could determine and then suddenly had a death event with symptoms compatible with digoxin intoxication, was found in fresh post mortem serum to have a concentration of digoxin in the vicinity of 70 nanograms per millilitre. All of these lead me to conclude that she did indeed receive a rather large dose of digoxin shortly prior to her death and that this was likely contributory to her death.

Complicating factors were that because of her underlying disease, her hypoxia and her inherent arrhythmia may have predisposed her to toxicity to digoxin to a greater degree than a child who did not have these complications.

Q. Thank you, Doctor. Doctor, with respect to the last known dose or prescribed dose of digoxin to have been received by this child, we have heard evidence from Dr. Robert Freedom, who was involved in the care of the child, that although earlier in the evening on March 20th when he left the Hospital he felt at that stage that it was likely not necessary that further digoxin be prescribed, that was not the view of other attending staff



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cardiologists and a dose of digoxin was administered that evening at 9:00 p.m.

A. On the 20th?

On the 20th the evening before her death. The amount of the dose was .032. Were you aware that that dose had been given to this child?

A. Yes, T believe so.

O. Doctor, as well with respect to the post mortem serum level and the toxicology data that you have outlined that was available from the Centre of Forensic Sciences, does that data assist you in this case in drawing any sensible conclusions or estimations regarding the likely time of administration of the drug and the possible mode of administration of the drug in this case?

A. Well, again we are struggling with concentrations in preserved tissues but even given that the concentrations are rather low, if one assumes that the concentration in the tissue was low even if we allow for the leaching of some of the tissue digoxin in the Klotz solution and we look at the serum concentration of 70, that suggests that she received a dose of digoxin within that time frame prior to her death which did not allow



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any significant degree of distribution into the tissues.

So, because of those constraints, I thought the most likely possibility was that she received a dose of digoxin within an hour or so prior to her death, therefore, not allowing any significant distribution to the tissues. That was the only way I could really account for these small amounts that apparently were present in her tissue.

Well, to be clear, Doctor, as to the concentrations that were in fact found in her tissues, you have told us as to what the range of concentrations were in the myocardium tissues. In fact, there were fixed specimens from the lung assayed as well and, as I understand it, no digoxin was detected in those specimens, is that correct?

> Α. That is correct, I believe.

0. And Doctor, you have told us as well I believe that at approximately 1:45 in the morning on the 21st of March this child's apex became irregular and she then began to gag and vomit. The medical record indicates that at 2:40 a.m. a dose of Lasix was given and at 2:45 a.m. she began having seizure-like activity and a Code 25 was called. Ultimately, after extensive resuscitation efforts,



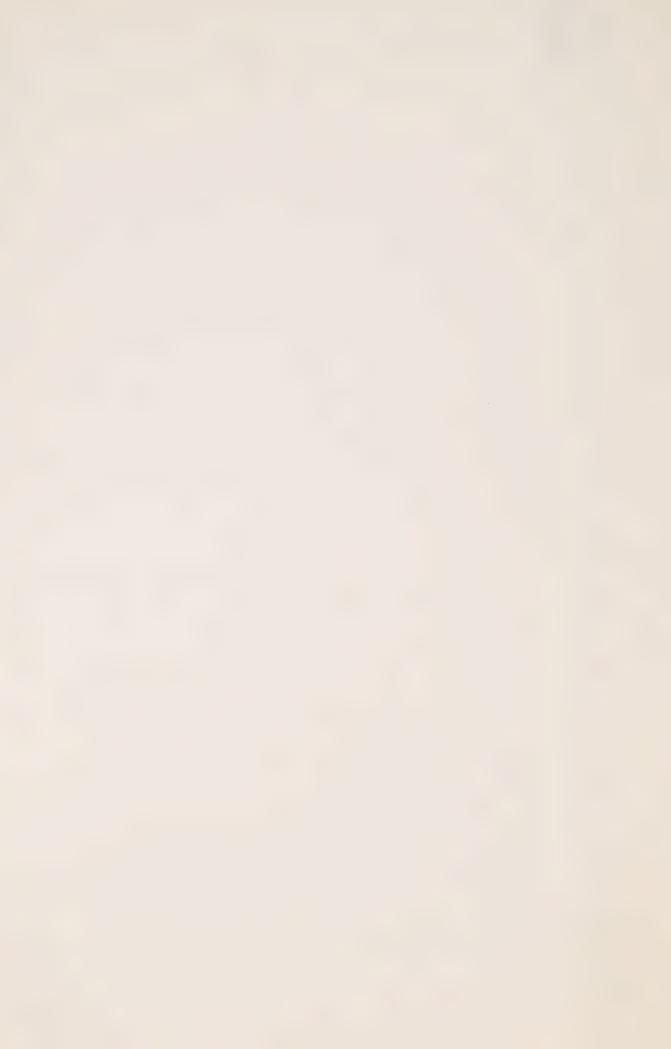
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the child was pronounced dead at approximately 3:27 in the morning. When you, Doctor, indicate that in your opinion the dose was likely to have been administered within an hour or so of death, what time are you referring to as the time of death?

A. Well, if I had to be more specific I suspect I would say that the administration was somewhere within an hour prior to the onset of the critical symptoms; in other words, the increased bradycardia, the gagging, the vomiting and then the seizure and so forth.

- Q. All right.
- A. I think those are all symptoms compatible with digoxin intoxication. So, that is the premise I am working on.
- Doctor, this may be something that you can help us with and it may not, but again, we have two time intervals here that are at least recorded in the progress notes. At 1:45 we see the irregularity in the child's apex and the gagging and the vomiting to which you have referred but it is almost an hour later well, it is indeed an hour later when it is noted that she began seizure-like activity. When you talk, Doctor, of the onset of the critical symptoms, do you have one of those

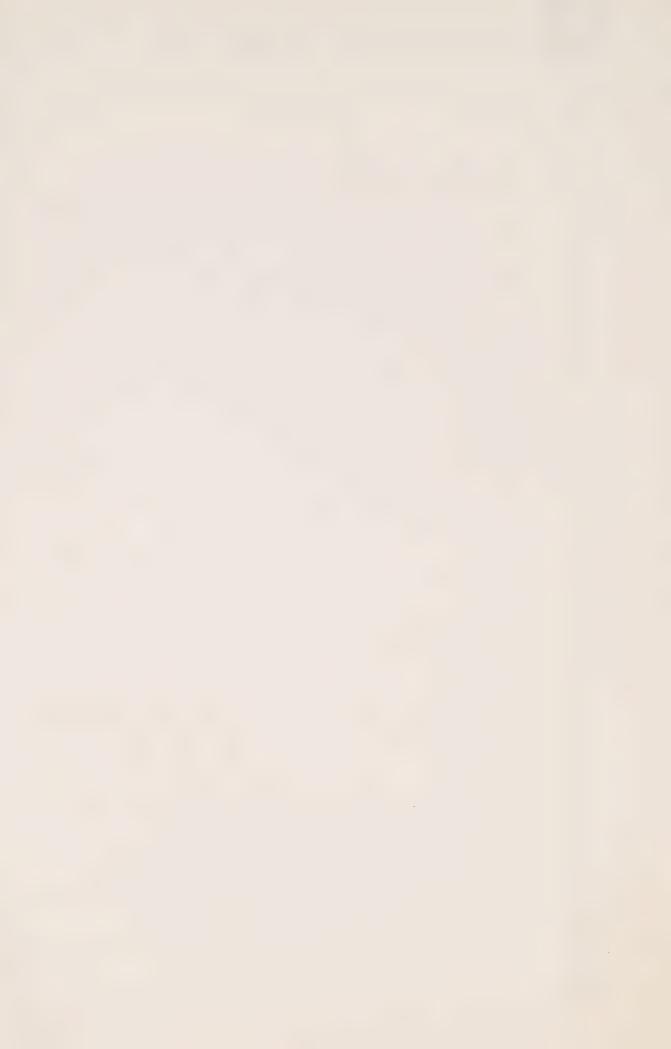


two specific times in mind?

A. Well, I was actually relating the onset to the increasing bradycardia and irregular heart rate and the gagging and vomitting. I think that could have been the onset of the symptoms that had progressed to the other symptoms that followed. There is a complicating factor and, that is, because of her rapidly deteriorating condition, the seizures could possibly be related not to digoxin but to lack of oxygen or ascidosis or other things that were intervening over that short period of an hour when she was rapidly deteriorating.

Q. Doctor, is it then your best judgment, bearing in mind that the gagging, the vomiting and the bradycardia that you have mentioned are recorded as having occurred or at least starting to occur at 1:45 in the morning, is it then your best justment that this dose would likely have been administered about an hour before that time?

A. I can't be precise about the hour but I would agree that it was most likely administered prior to the onset of those symptoms which appear to be the beginning of a series of worsening symptoms. It could have been as early as 30 minutes, maybe probably within an hour.





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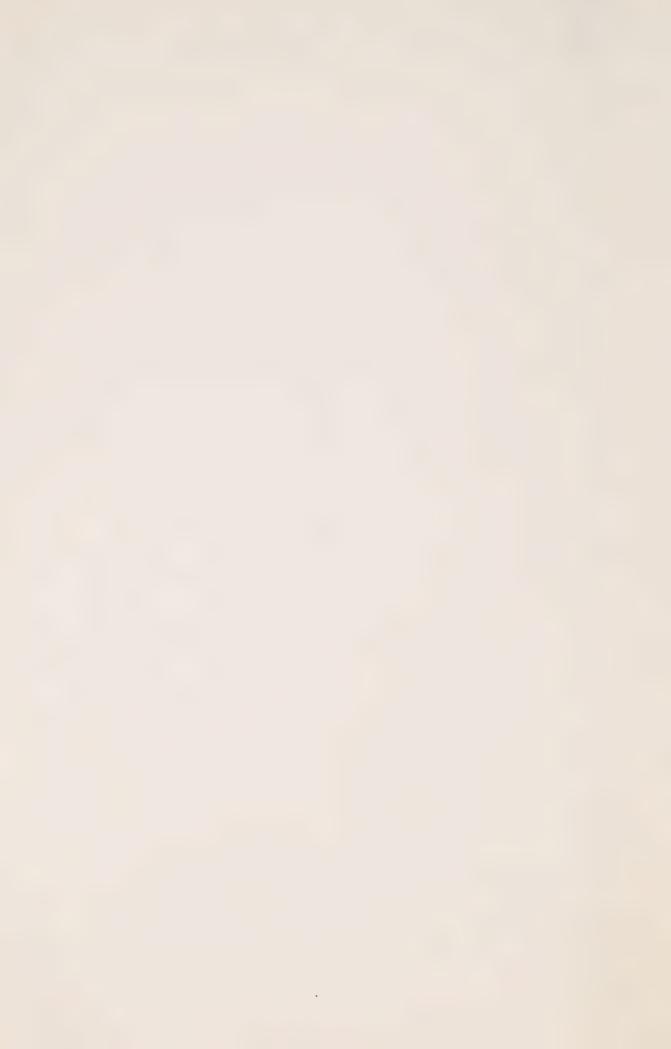
Q. All right
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I said in my report, I gave out side numbers of 60 to 90 minutes to be generous but I really believe it was probably shorter than 90 minutes.

0. All right. Doctor, if the dose had been administered for example an hour and a half prior to the onset of those critical symptoms would you in those circumstances expect any discernable distribution to tissues?

I would have expected even in preserved tissues more digoxin, measureable digoxin there particular in the lungs because if the drug is administered intravenously, for example, all of the cardiac output goes through the lungs. Although this child did have an anomaly which changed that to some degree but it really didn't reduce the amount of blood that was going through her lungs, it actually increased it. So, I would expect that length of time to allow some equilibrium with lung tissue.

Doctor, in addition to 0. expressing an opinion in your report as to the likely time of administration of the drug, you as well addressed the issue of the likely method of





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administration, did you not?

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on, ara you not:

A. Yes, I did.

Q. All right. And as I understand it, Doctor, your best opinion in that regard is set out on page 6 of your report in the first full paragraph and you have indicated that the tissue levels and the serum level are consistent with a large intravenous bolus injection. Do I have that correctly, Doctor?

A. Yes, that is correct.

Q. Doctor, if we fairly infer, as you have suggested from the low tissue concentrations in the heart tissues and from the absence of identifiable concentrations in the lung tissue that there was a minimal amount of distribution of digoxin from serum to tissue in this case, is it possible in your view that the dose of digoxin in whatever quantity it might have been could have been administered within an hour of the actual Code 25 called on this child. Could it have been later than the time frame you have estimated?

A. I think it is somewhat unlikely looking at the undetectable amount of the tissue. I think in the sample of the lung there was not any digoxin found either in the lung or in



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1 2 the Klotz solution in which the lung had been fixed. 3 0. That is correct, Doctor. 4 So, we have to assume that 5 there was no significant quantity of digoxin in that tissue. So, I think that the digoxin must have been 6 administered within a relatively short time prior to the infant's death. 8 THE COMMISSIONER: I think the 9 question was the opposite way around. 10 MS. CRONK: That's right. 11 THE COMMISSIONER: Whether it could 12 have been shorter - it could have been closer to the ---13 THE WITNESS: Shorter to the ...? 14 THE COMMISSIONER: To one hour. 15 THE WITNESS: To one hour. Yes, 16 it could have been shorter than one hour, yes. 17 MS. CRONK: Q. And still result 18 both in those symptoms and that serum level? 19 Α. Yes, I think so. 20 And the concentrations in the Q. tissues? 21 Α. I believe so. 22 0. All right. Doctor, as I 23 understand it as well in your report you attempted



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as best you could to estimate the minimum possible dose that could have been administered to the child and yet achieve those digoxin levels, is that correct?

- Α. That is correct.
- 0. And what was the minimum dose in this situation, Doctor, that you estimated?
  - Approximately .5 milligrams.
- And if we refer both to your first and your second reporting letter, Doctor, as I understand it, you have indicated that that amount of a dose would require approximately 11.1 millilitres of the pediatric intravenous injectable preparation?
  - A. That is correct.
- And similarly it would require in your view, if I have it correctly, a volume of 2.2 millilitres of the adult intravenous preparation?
  - That is correct. Α.
- 0. And as well you estimated with respect to the oral elixir that it would require a volume of 11.1 millilitres?
  - That is correct. A.
  - Q. Do I have that correct?
  - That is correct also.

THE COMMISSIONER: Those figures translate into vials which are a lot easier for me,

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ll pediatric and a little over 2?

THE WITNESS: One adult and 11

pediatric.

THE COMMISSIONER: One adult, oh,

yes.

THE WITNESS: The adult is a

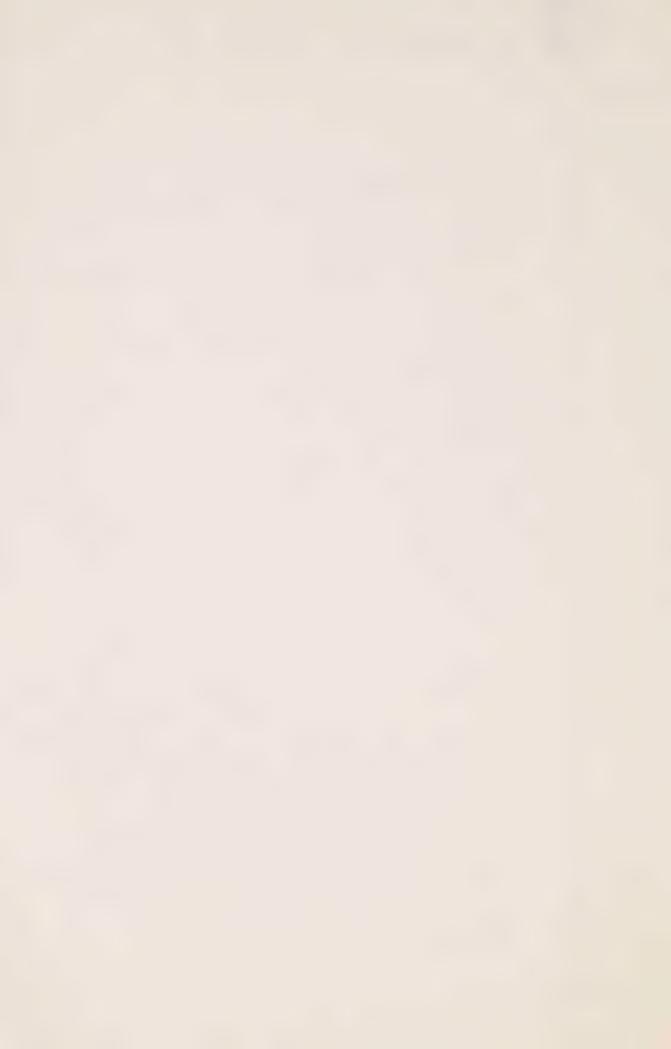
2 millilitre vial.

THE COMMISSIONER: Yes, all right,

thank you.

MS. CRONK: O. Doctor, in making that estimation I assume as you did in other cases that you were required to make certain assumptions regarding the method and type of administration that applied?

- A. That is correct.
- Q. Could you briefly outline for us, Doctor, please the assumptions that you made?
- A. I assumed as you said that there was no distribution from the central compartment so I again used the central compartment volume of distribution of 1.3 litres per milligram. The infant's weight was 6.11 kilograms. The concentration I assumed was 70 nanograms per millilitre and multiplying that all out it comes out to be .556 milligrams.





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All right. Those assumptions, Doctor, I take it are essentially the same as those which you made with respect to Justin Cook in estimating his minimum dose?

That is correct.

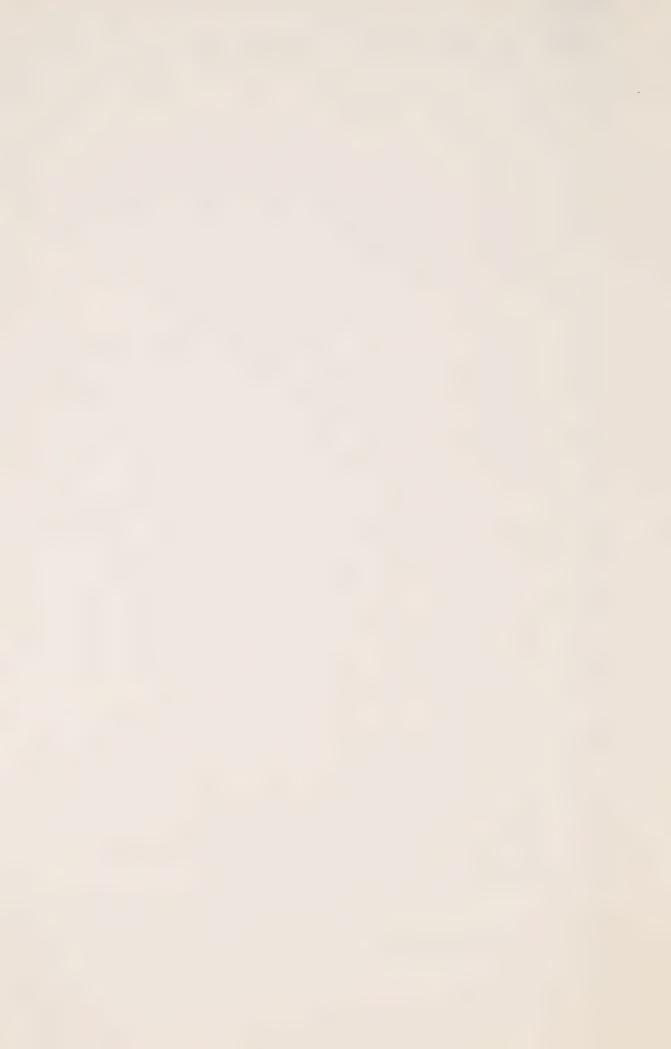
0. All right. Doctor, having regard to the fact that that was a minimum estimation that you made based on those assumptions, can you help us as to what level of confidence you place on that minimum estimate?

I can't put a number on it. I think that represents close to the least it could be unless one wanted to accept a smaller volume of distribution then you come out with a number that was somewhat smaller than that. The dose - I don't have a great deal of competence that the dose could not have been somewhat greater than that.

Q. How likely in your view, Doctor, is it that the minimum dose scenario applied?

I think in view of the fixed tissue concentrations that that is the most likely possibility in opposition to a dose some hours earlier allowing tissue distribution.

0. All right. Doctor, you have expressed the opinion in your report, as I understand



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it, that it is highly unlikely that digoxin in this case was administered orally. Do I have that correctly?

- Α. That is correct.
- 0. And that is as well found

at page 6 of your first reporting letter?

Α. That is correct.





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Q. Can you help me please, Doctor, as to the basis upon which you rejected oral administration as a likely candidate?

A. Again one of the factors was the volume required in a child who was not taking feedings well and was having difficulty keeping things down.

Secondly, when the drug is given orally it takes a while for it to be absorbed, and the reported time to reach peak levels after an oral dose, reported in the literature, is approximately one to two hours.

Q. I am sorry, Doctor?

A. One to two hours for peak concentrations in serum after an oral dose. Of course distribution and excretion and everything else is going on simultaneously. So to achieve a high serum concentration as we see here with minimal tissue distribution it is harder to reconcile with an oral dose where you have to allow time for absorption to reach concentration.

Q. Would that be so, Doctor, regardless of the amount of the elixir that might have been administered?

A. Yes.

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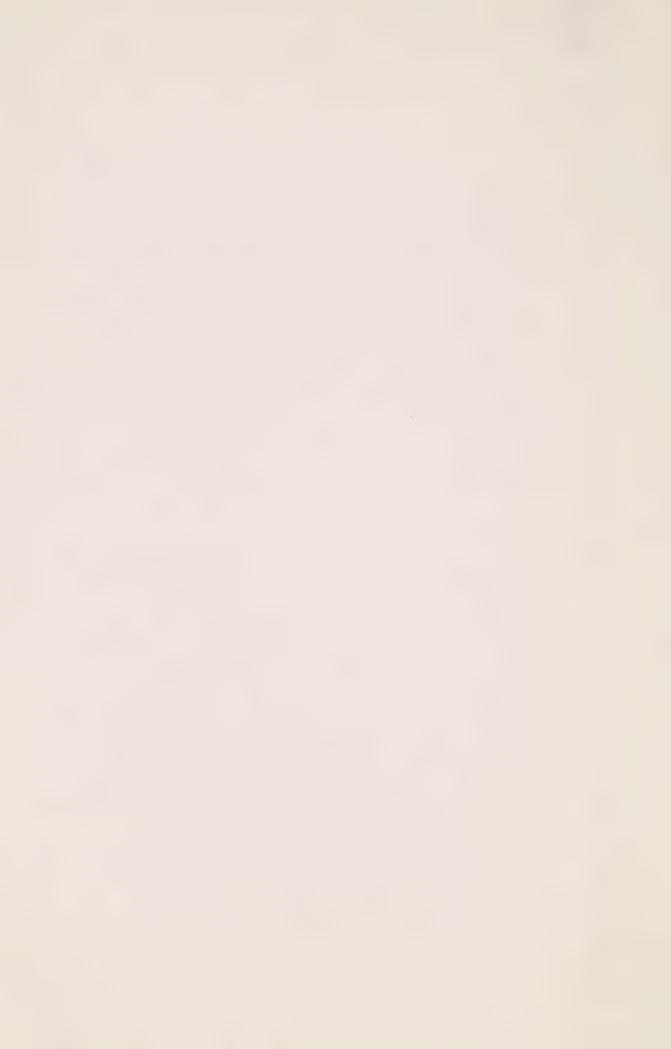


Q. Doctor, as you will recall from earlier this morning we have heard extensive evidence from Dr. Speilberg concerning this child amongst others; and you will recall as well that according to the medical record of this child lasix was given at 2:40 a.m. in the morning. I direct your attention, Doctor, to page 115, if you would please of the medical record.

- A. I am sorry, what page?
- Q. 115; I'm sorry, page 42,

Exhibit 115, do you have that, Doctor?

- A. Yes.
- Doctor, the nursing note made
  by Nurse Nelles on March 21st, 1981 starting about
  two-thirds of the way down the page for the period
  1:45 a.m. to 3:27 a.m. indicates that at 1:45 as we
  noted earlier the child's apex was irregular. It
  happened three or four times. The child began to gag
  and vomit large amounts of very thick clear mucus.
  She was suctioned for further amounts of this mucus.
  Dr. Soulioti came to examine the child and administered
  lasix, 6 milligrams IV push at 2:40 a.m. At
  approximately 2:45 the babe began to seizure and
  become very rigid with extended legs and arms. On
  oscillation there was no heart rate, CPR was initiated



and a Code 25 was called.

You see, Doctor, from the progress notes that within five minutes of the administration of what was recorded to be lasix seizure like activity ensues, heart rate disappears and cardiopulmonary resuscitation is immediately commenced.

Doctor, in your view, having regard to the amount of lasix that is recorded as having been administered, if digoxin had been mistaken for the lasix dose which was intended to be given, could 6 milligrams of digoxin given by IV push account both for the symptoms which then ensued and the cardiac arrest of the child as well as the level of digoxin found in the serum concentration post mortem?

I would have to know - I don't think we know from the chart what was meant by IV push, whether the medication from the syringe was actually attached to the needle at the baby's vein and pushed in within a few seconds; or if it was pushed in in the lower part of the IV tubing just above the vein and over what time was it actually pushed in, whether it was a few seconds or maybe a minute or what they meant by IV push.

The reason that poses a problem is that



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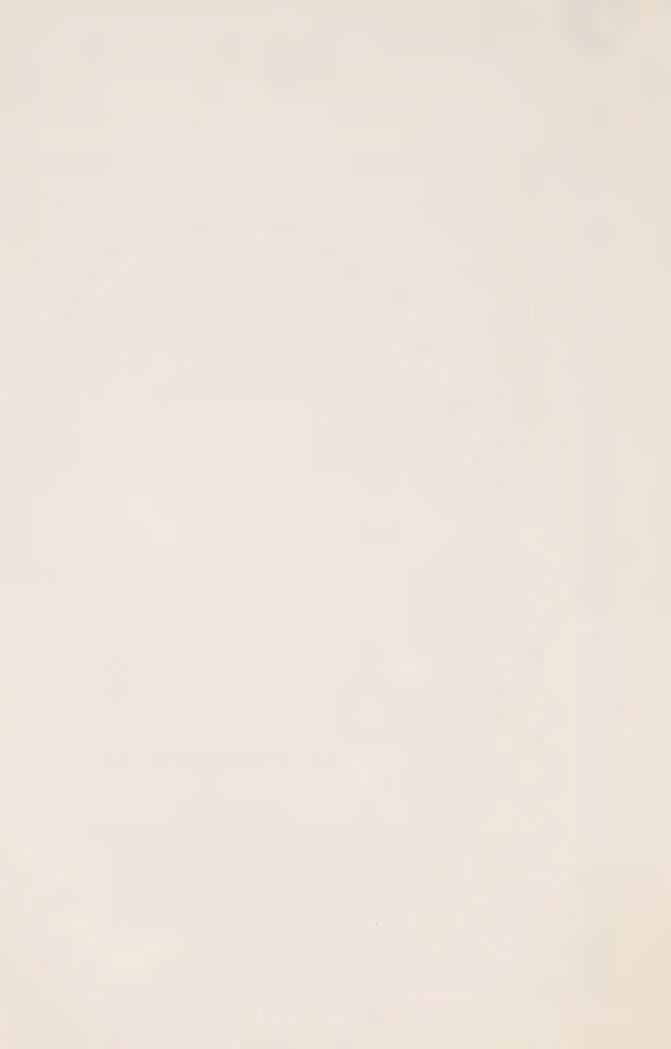
if it was put in the IV tubing even a few centimetres above the vein, and I don't know where the ports were in this particular set-up, there would occur some dilution and then there would be some delay probably a few minutes of it completing to infuse to the baby, being on the IV flow rate. If it was pushed rapidly right into the vein at the hub of the needle then it would have gone in somewhat more rapidly, so I don't know those variables.

Now looking - and that determines what kinds of concentrations you might predict in the serum.

In looking at the volume of lasix that was given to provide 6 milligrams, I think lasix comes as a preparation of 10 milligrams per millilitre, so 6 milligrams would be in the volume of .6 millilitres. If one administers .6 millilitres of digoxin as a paediatric preparation and multiplied .6 times .05, what is it ---

0. The concentration of the paediatric ---

A. No, the amount, I am trying to get to the amount of digoxin, I would have to do my arithmetic before I can answer your question, just a moment; that would have been .03 milligrams.



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If the adult preparation was given that volume would contain .15 milligrams. So then we need to see what concentration might be produced in a relatively short time depending on how much distribution had taken place. If you put that amount of digoxin into a volume of 1 litre per kilogram, and this baby weighed - I am sorry, I have lost the weight.

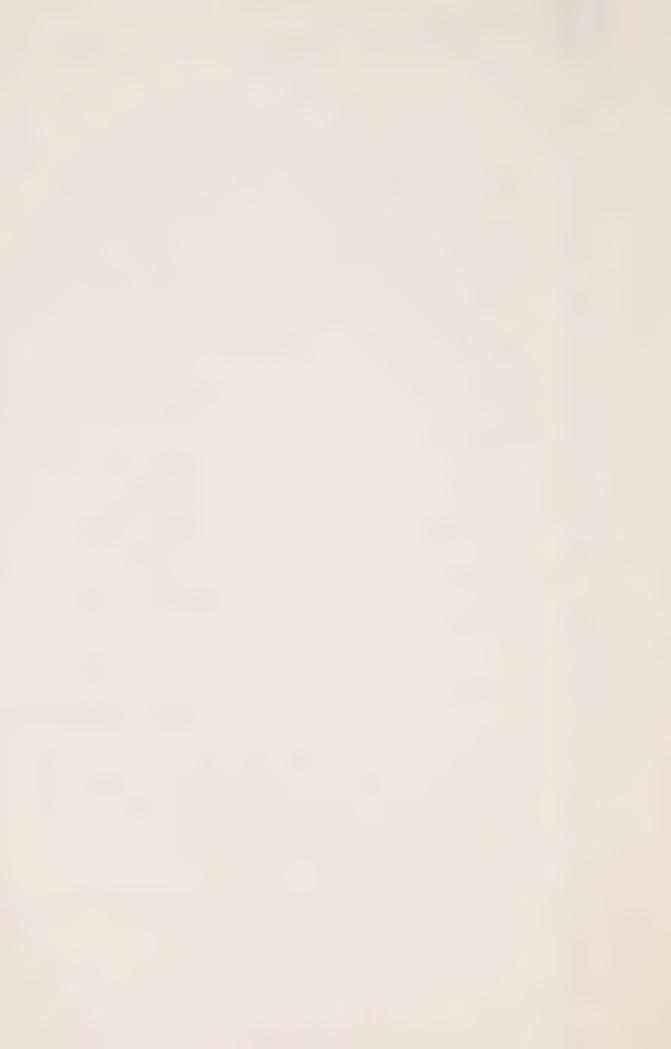
At the time of death, Doctor, she weighed 6110 grams.

Okay, 6 kilograms. 6 kilograms divided by .15 - I am sorry - you could conceivably have a concentration in the range of 25 if you injected adult IV digoxin into that volume, that volume of digoxin into this apparent volume of distribution.

What, Doctor, if the paediatric Q. had been used - I am sorry.

Well if the paediatric had been used it would be much much less than this. The point I am making is that it is hard for me to explain the serum concentration of 70 based on that kind or dose if that kind of error was made, that is all I am pointing out.

MR. STRATHY: May I just ask a question,



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it might be convenient to ask it here.

THE COMMISSIONER: Yes.

MR. STRATHY: Doctor, you said it

could lead to a concentration of 25?

THE COMMISSIONER: That is nanograms

I take it per millilitre.

THE WITNESS: Per millilitre.

MR. STRATHY: After the injection?

THE WITNESS: Yes.

THE COMMISSIONER: That is at the

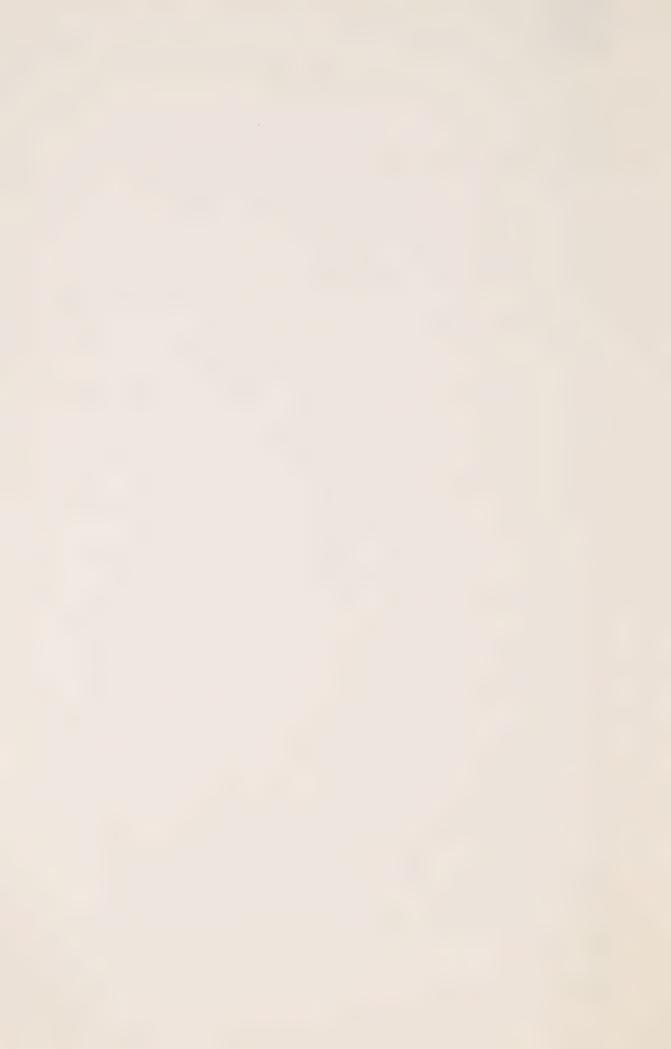
height of the alpha phase?

THE WITNESS: Yes.

MR. STRATHY: That is ante mortem?

THE WITNESS: Well I am assuming -

yes, it was injected ante mortem. I am assuming now that the baby was alive, I don't know the exact circulatory status except it wasn't ideal at the time that this, 2:40 a.m., but assuming at the time it was actually injected that there was still a heart rate and that distribution did take place, the circulation time ordinarily is about 12 seconds with normal cardiac output but this child was probably prolonged somewhat, but five minutes would allow mini circulation time for the drug to get to the lungs and distribute into the high blood flow organs



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which comprise the central compartment.

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MS. SYMES: Doctor, could you again give the calculation that you did to achieve the 25 nanograms per millilitre please.

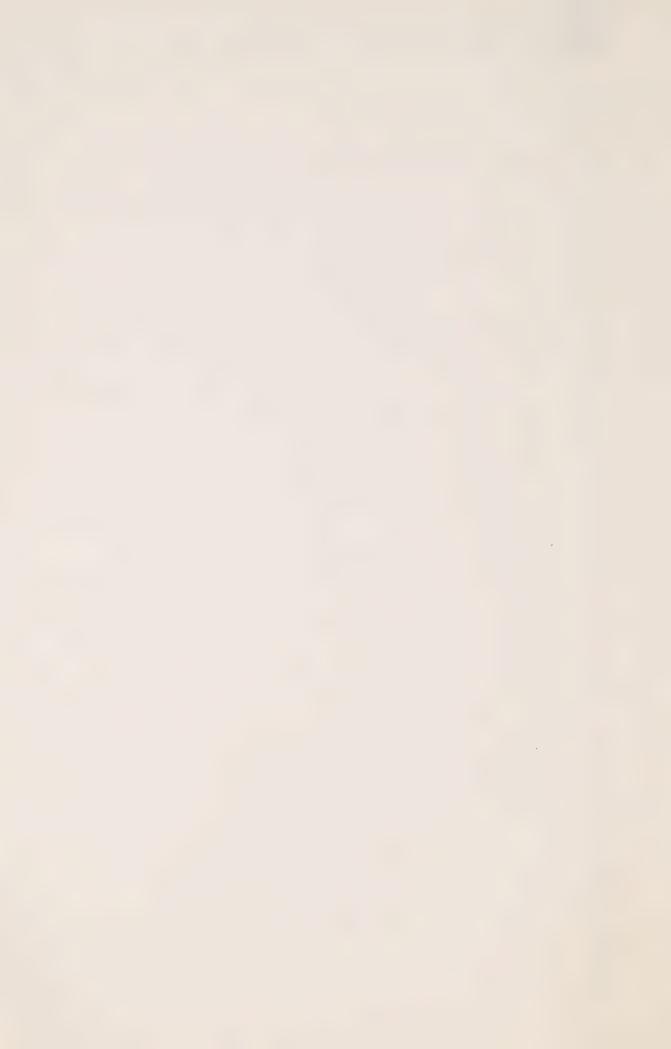
THE WITNESS: Okay. If digoxin had been mistakingly placed in the syringe rather than lasix; and if indeed the dose of lasix that had been ordered, the same volume for that dose had been drawn up in the syringe, i.e. .6 millilitres, and the mistake was with adult intravenous digoxin, that would provide 150 micrograms of digoxin in that .6 millilitres. If that was rapidly injected, and over the next five minutes the child maintained circulatory status so that the drug could be carried to the high blood flow organs, that is the lungs, the heart, the liver, the kidney primarily, then we can assume a volume of distribution in the range of 1 litre per kilogram to make it easy. If you divide and the baby weighed 6 kilograms, so that is 6 litres into which that 150 micrograms would distribute, and if you divide 6 into 150 you get 25.

MS. SYMES: Thank you.

THE WITNESS: Is that clear?

MS. SYMES: Yes, thank you.

MS. CRONK:  $\Omega$ . Doctor, if we assume





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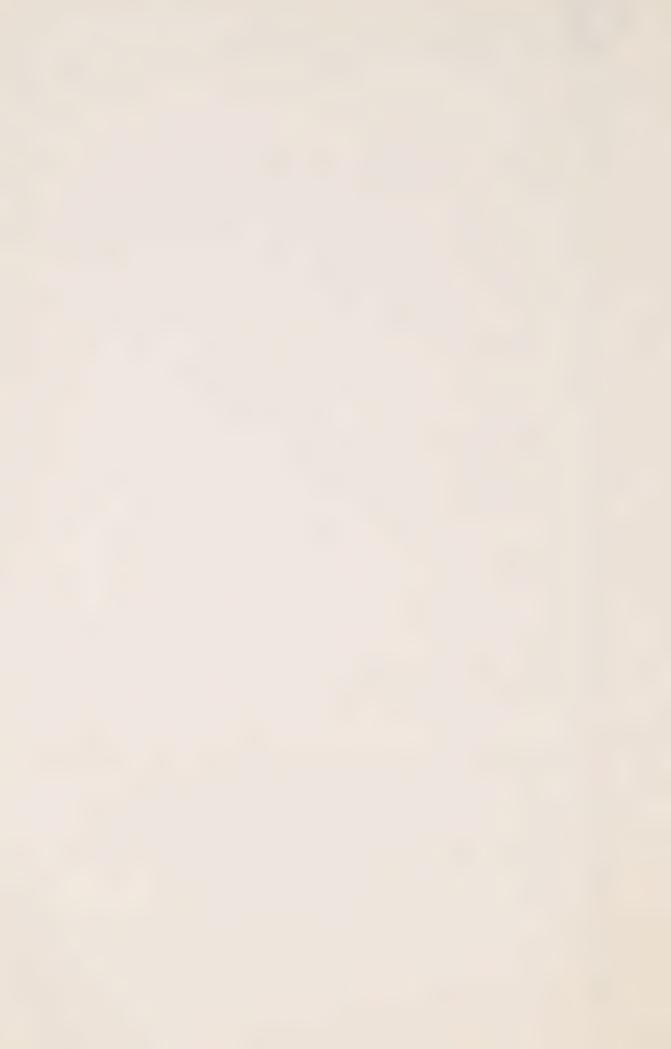
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that the dose was in fact given in that way, and that an adult ampule was mistaken, or was given to the child be it accidentally or intentionally at that stage, are you saying then that given five minutes of relatively free circulation time an ante mortem level of digoxin of 25 nanograms could have been achieved?

- It could have been.
- 0. And were that to be the case, Doctor, would that account in your view for the digoxin concentrations found in the myocardium tissues after death?
- The myocardium with fixed Α. tissues?
  - 0. Yes.
- Α. It wouldn't be inconsistent with that, no, because we are saying that there was no distribution to the tissues essentially.
- Q. And as well, Doctor, if that were the case and an ante mortem level of 25 nanograms had resulted, if we apply the post mortem multiplier about which you have spoken earlier, you have told us that the range in your view can be anywhere from 1 to 4, do I have that correctly?
  - Α. That is correct.



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Q. If that is the case then with
the application of a post mortem multiplier within
the range which you considered to be acceptable, we
could account for the post mortem serum level found
in this child, could we not?

Multiplier of three fold which I think is in the realm of possibility without any tissue distribution and obtaining the sample as early as six hours after death, I think that is somewhat unlikely. Because as I said yesterday the multiplier is somewhat related to the time after death that the sample is obtained. So I think it is in the realm of possibility. I think it is somewhat unlikely.

 $\Omega$ . Doctor, are you aware of the forms in which lasix was available on these wards in March of 1981?

A. No, I am not other than I know that the IV preparation had that concentration in it but I don't know ---

Q. I am sorry, Doctor.

A. I am not familiar with the Canadian product.

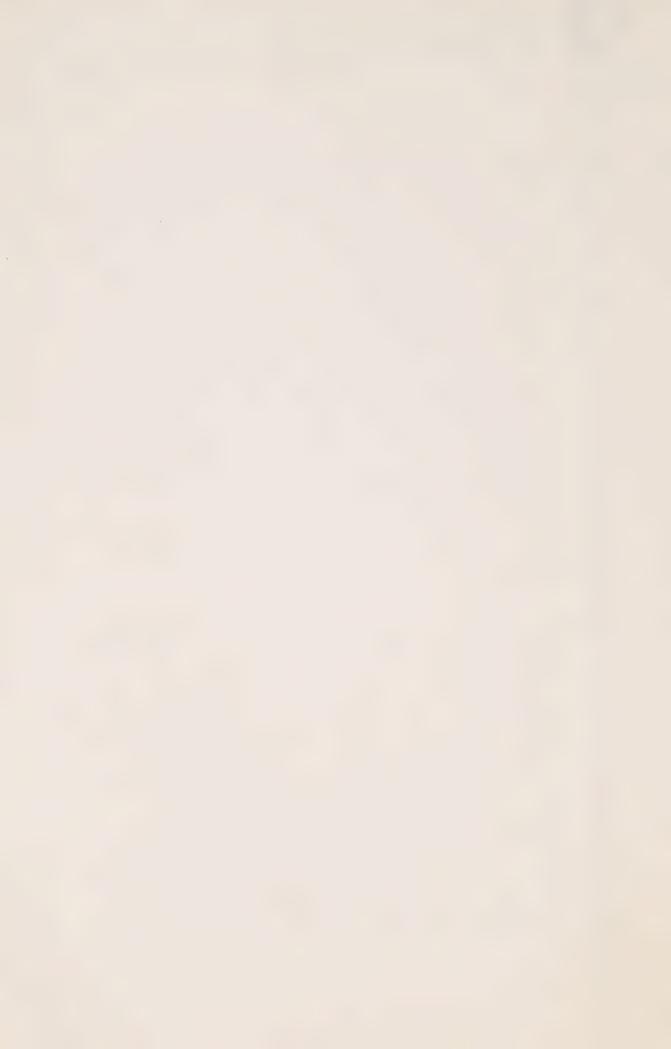
Q. Leaving aside the issue of volume and concentration, I can tell you that the



evidence before the Commissioner has demonstrated that the ampules of lasix which were available on the ward and which have been marked as exhibits here, come in a brown coloured ampule; while digoxin in both the paediatric injectable preparation and the adult injectable preparation come in a clear glass ampule. The size and shape of both the lasix ampule and the digoxin ampules are the same. The lettering on the two different kinds of drug vials is different, in different colours. Are you in a position, Doctor, to express any opinion in the face of the facts as to the likelihood of a vial of digoxin, be it adult or the paediatric, having been confused for a vial of lasix?

A. Again I think I would have to say that it is possible. I think it is improbable because of the difference in colour and these were medications that were apparently commonly used on this ward. The people preparing them and administering them were not drug naive people, they were people who were quite familiar with these different preparations, experienced nurses and physicians.

So I think it is somewhat improbable that that kind of difference that you described in appearance of the vials that they would have been mistaken one for





2 the other.

of hospitals?

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Q.	Doctor, I take it though that
ou would have no	difficulty in agreeing that
medication errors	whereby one drug is mistaken for
nother do in fact	

A. They certainly do.

Q. Even in the most sophisticated

A. That is right.

MR. SCOTT: I take it just so that we will be clear that the Doctor's explanation is one based on his study of human nature rather than based on his study of pharmacology, when he has said that this is impossible - he didn't say impossible he said less than probable. My friend is not soliciting a pharmacological explanation from him for that. Have I got right what the witness is saying?

THE COMMISSIONER: I would have thought it was the combination of everything, including his pharacological ability, I think he understands what goes on in hospitals.



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MR. SCOTT: No, he goes on and he concentrated on the colour of the vials and so on and so forth, making it less than probable.

THE COMMISSIONER: I thought that the conclusion of probability was based on all the observations in his life including his professional life but perhaps I am wrong.

MR. SCOTT: No, maybe I am wrong.

I just thought that we departed from pharmacology
to human nature rather quickly.

THE COMMISSIONER: Well, I thought we took hold of both.

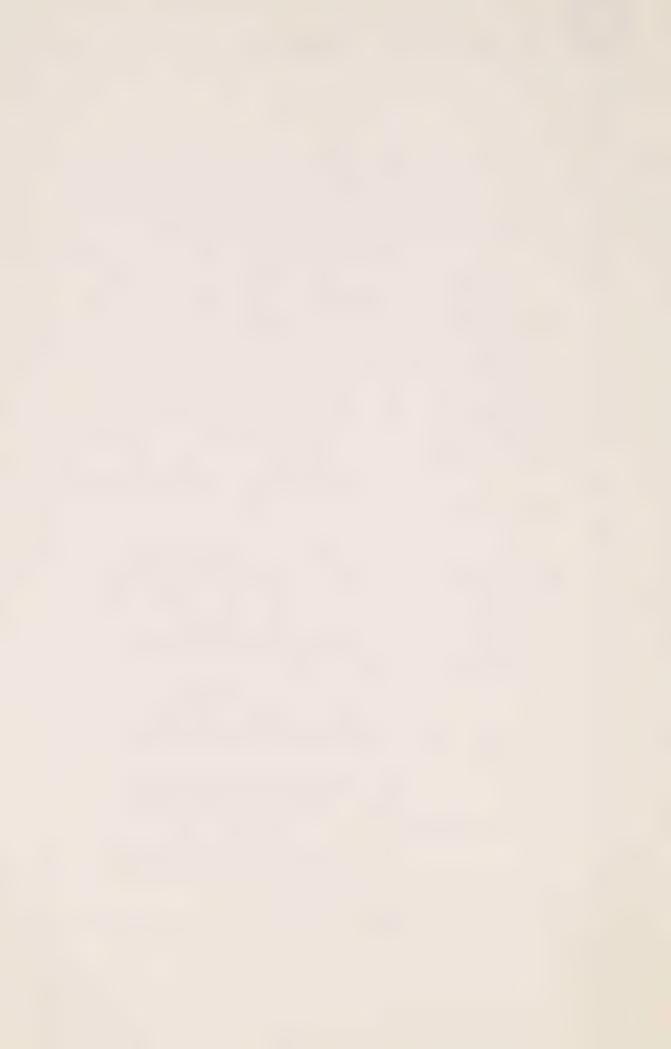
MS. CRONK: Q. Well, doctor, in fairness to you I certainly didn't ask you whether you were -- in putting that question I didn't ask you whether you were basing it on a particular experience based on your life.

To be fair to you were you expressing that -- how were you expressing that opinion?

A. I hadn't considered the difference, frankly.

Q. I wouldn't have thought so,

Doctor, I take it in your experience



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in the hospitals in which you have worked you have had occasion to be exposed to medication errors which do occur with pediatric patients?

- Α. Yes, I have.
- Ω. Have you as well over the years. doctor, had experience and become familiar with medication errors which occur with infants whereby one drug is confused and mistakenly administered for another?
  - I am aware that that occurs.
- Q. And as well, doctor, where a drug prescribed for another patient in certain situations can be inadvertently administered to the wrong patient?
  - Α. Yes.
  - 0. Errors of a number of kinds?
  - Α. That is right.
- Doctor, we have heard Q. evidence as well from Dr. Spielberg as to his concerns regarding the circumstances of the death of this child.

He has told us and this evidence is found, Mr. Commissioner, at Volume 55, page 2228, that if digoxin in fact was given at 2:40 in the morning or there abouts instead of Lasix to this child



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the child in fact might have died of propylene glycol toxicity before she died of toxicity from the digoxin.

He has told us as well that injectable digoxin in the form that was available in this Hospital at the time is 40% propylene glycol.

Are you able, doctor, again under the scenario which you have posited for us, assuming that digoxin was administered in lieu of the Lasix and that it was an adult ampoule of digoxin involved in that process, are you able to express any opinion for us as to whether or not the propylene glycol in that amount of digoxin would be sufficient to cause the death of this child?

A. I would like an opportunity to explain my answer, but I think it is unlikely, but I would like to tell you why if I may.

 $\Omega$ . I would like you to do that, doctor. Yes. Thank you.

A. Again, we need to do some arithmetic to work this out.

It is true that digoxin as well as many other drugs that are not very soluble in water which need to be placed in solution for intravenous administration contain propylene glycol as part of the



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solution along with alochol, and the reason for this is that propylene glycol is one of the alcohols which has been thought to be relatively innocuous and harmless because it is metabolized by normal metabolic pathways in the body so it exists in various water soluble preparations.

So it is true that to my knowledge the digoxin intravenous solution contains 40% propylene glycol.

If indeed this mistake was made and .6 millilitres of digoxin solution rather than Lasix was administered intravenously, and that contained 40% propylene glycol, then the patient would receive .24 millilitres of propylene glycol intravenously.

I may not be aware of all the literature on propylene glycol toxicity, but what I am aware of can be summarized as follows:

The major toxicity from this drug has been described after oral ingestion in very large amounts or chronic repetitive ingestion in some medication of rather large amounts or in infants getting intravenous total feeding containing multiple vitamin preparations containing relatively large amounts of propylene glycol to keep the fat soluble vitamins in solution.



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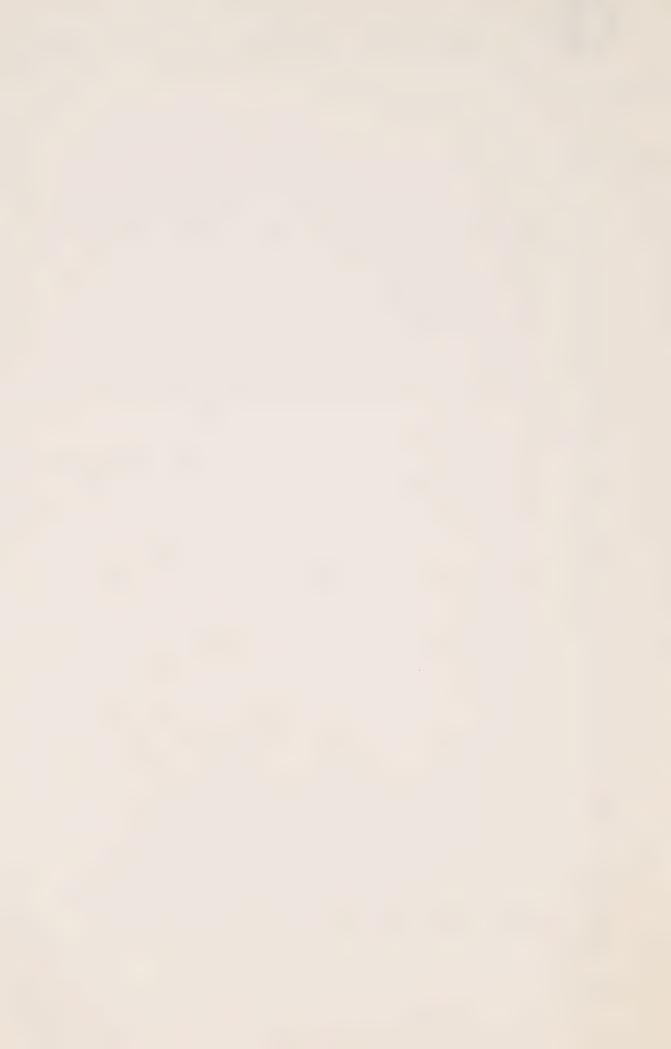
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In these cases the symptoms of toxicity have been primarily central nervous system depression and/or seizures and metabolic acidosis due to lactic acidosis because propylene glycol can be metabolized with lactic acid and if the child doesn't have any capacity to metabolize the lactic acid that is enough to produce toxicity from that. That is what happens with the vitamin business.

There are case reports in the literature of children being intoxicated because they received over a period of weeks orally or by total parenteral nutrition large amounts of propylene glycol.

aware of is an animal experiment in cats in which propylene glycol was injected rapidly intravenously and it could be demonstrated if amounts -- these people gave as I recall about .5 to 2.5 millilitres per kilogram to the adult cats and they injected this within one to five seconds intravenously and they could produce profound drop in blood pressure, slowing of the heart rate, irregular heart rate and various sorts of heart abnormalities, rhythm abnormalities and in some cases stopping breathing.

This is a relatively large dose and is much larger than this dose. If you divided this



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by 6 you would get a dose in terms of amount per kilogram of .04 millilitres per kilo in this scenario.

So the amount is about 10 to 25 times the animal experiments, this one that I am aware of, to what could have occurred in this particular situation.

So I have a difficult time accepting the probability that this kind of error could have caused cardiac arrest and damage to the infant based on this kind of dose of propylene glycol.

I know from personal experience that we not uncommonly give drugs containing this quantity of propylene glycol intravenously to treat seizures and for other indications intravenously, and it is done fairly frequently without seeing direct cardiac toxicity. So I think because of the possible dose related to what has been shown to be acutely toxic, at least in the animal studies, that it is somewhat unlikely.

Thank you, doctor.

Doctor, if we assume that a larger amount of digoxin was given instead of the .6 millilitres that we have posited, I take it that would therefore proportionately increase the amount of



EE7 2

propylene glycol available to achieve a potentially toxic effect in the child?

A. Yes, I think so. If you are willing to accept 5 to 10 times that amount, then I think that might be a more probable hypothesis.

Q. And, doctor, can we as well agree that were that to be the case -- were that to be the case, doctor, that would necessarily involve two medication errors: the first being that digoxin in the first instance was mistaken for the Lasix that was intended to be given. That is the first error that would have occurred?

A. Yes.

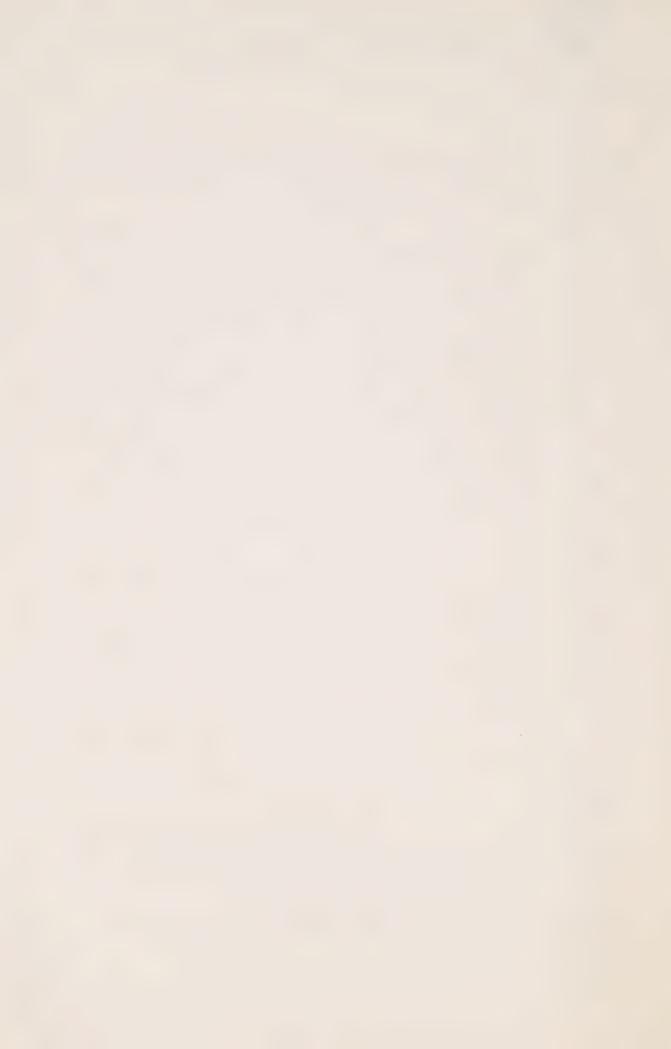
Q. Secondly, doctor, that the amount that was in fact given would have had to be mistaken -- I'm sorry, a mistakenly larger amount would have had to be given than the amount that was intended to be given were it Lasix?

A. In my opinion it would have to have been a considerably larger amount.

 $\Omega$ . Right.

THE COMMISSIONER: If you did give 5 to 10 times the quantity, you are obviously giving an overdose of digoxin?

THE WITNESS: That is correct.





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EE8 THE COMMISSIONER: Which would kill the child first? THE WITNESS: I have no idea. It might be a race. MS. CRONK: Mr. Commissioner, may we as well race for our break? THE COMMISSIONER: Yes. Fifteen minutes. MS. CRONK: Thank you. --- recess. 





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--- Upon resuming.

THE COMMISSIONER: I would just like to say for the benefit of counsel that there seems to some trouble tomorrow morning, not only Mr. Strathy but also Mr. Scott. Miss Cronk thinks that she might finish some time in the middle of tomorrow, so, I hope that there will be other counsel available to keep us going until the others arrive. So, don't expect that you will necessarily be spared until tomorrow afternoon, that's all.

Yes, all right, Miss Cronk.

MS. CORNK: Thank you, sir.

O. Dr. Kauffman, we have heard in evidence with respect to Allana Miller that this child evidenced at autopsy a significant degree of muscle damage caused, it was thought, by resuscitation efforts that were undertaken. I take it in this case you have seen the autopsy results on Allana Miller as contained in the medical record?

A. I have seen it but I haven't looked at it recently.

O. All right. It has also been suggested in evidence, Dr. Kauffman, again by Dr. Spielberg, this is found, Mr. Commissioner, at Volume 56, page 244, that the damage affected in this



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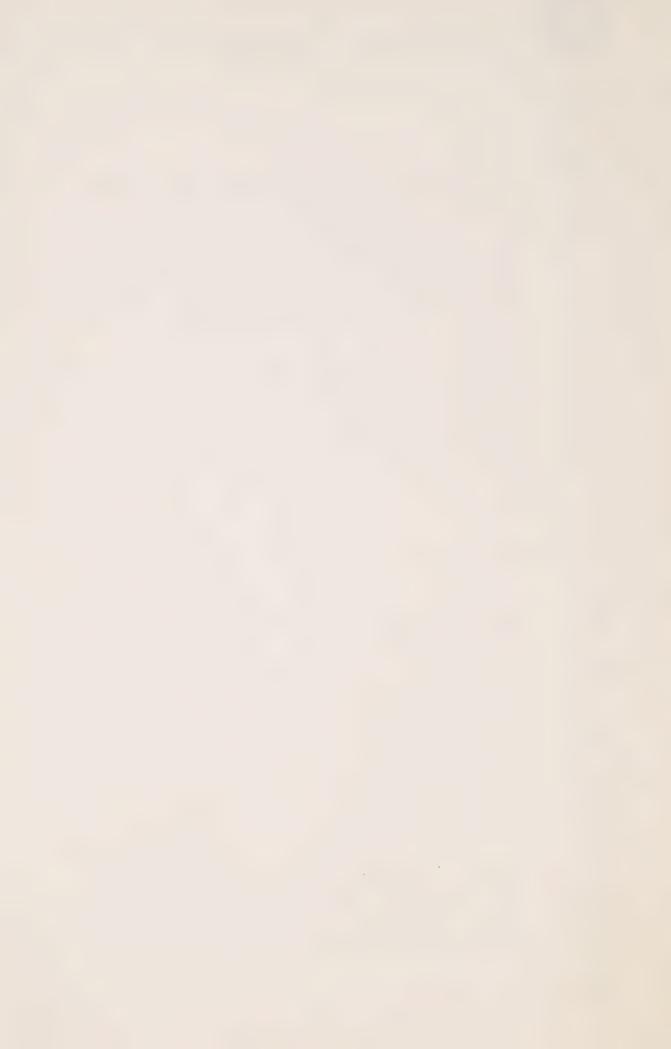
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way, that is, through the resuscitation effort could have had the result of dislodging digoxin from the cardiac muscle into the serum, thus resulting in an elevated digoxin level post mortem in the serum of the range that is found in this child.

As a pharmacologist, Doctor, do you ascribe to the school of thought which suggests that resuscitation trauma may in certain circumstances effect that kind of unbinding of digoxin from tissues during life?

A. Well, I think we have to accept that the ascidosis and the hypoxia that intervenes at the time of cardiac arrest and possibly also the potential trauma that occurs during cardio-pulmonary resuscitation could potentially change the distribution of digoxin from the heart, I think that is a possibility. It is hard to say to what degree in a given case but I agree that it is a possibility.

Q. Doctor, I would ask you to refer if you would please to page 41 of the medical record of Allana Miller. There is in this case unfortunately not as many particulars provided in the medical record concerning the steps undertaken





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in the resuscitation effort as there are in several of the other medical records that we have looked at.

But beginning at the bottom of page

41 we see the assistant resident's note as to the

events which took place during the resuscitation.

He indicates that the child was in extreme bradycardia

initially, leading to complete asystole. The child

was intubated after, I think it is a dose of

atropine by the anaesthetist and then despite repeated

- I'm not sure of the next word, it doesn't appear

to be doses - of atropine and various other drugs.

- A. Boluses.
- Q. Boluses of various other drugs including atropine, spontaneous electrical can you help me with the next words.
  - A. Potentials never returned.
- Q. Pupils were fixed and diluted and a pacemaker was also inserted by Dr. Schaffer with no effect. The child was then pronounced dead, according to his note, at 3:30 a.m.

In those circumstances, Doctor, bearing in mind that there were findings at autopsy of muscle damage, that is to the myocardium muscle, is it possible in this case in your view that there couldhave been that kind of unbinding of digoxin



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from cardiac muscle tissue so as to result in an elevation of the serum digoxin level in the child?

A. Before I answer that I would really like to look at the autopsy report again and see specifically what kind of damage was described and to what extent.

- Q. All right.
- Because I don't remember the details. Can you guide me to it?
- Q. I will, Doctor, as soon as I can find it.

MR. OLAH: Page 52, Doctor.

THE WITNESS: Page 52.

MS. CRONK: Thank you, Mr. Olah.

Q. We see, Doctor, under the Anatomical Diagnoses section of the first page of the autopsy report that Item No. 5 is resuscitation associated trauma with a number of specific items then outlined?

A. Okay, that's helpful, thank you.

> You are welcome, Doctor. 0.

My question, Doctor, was in this specific case, having regard to what is described as having taken place during the resuscitation effort



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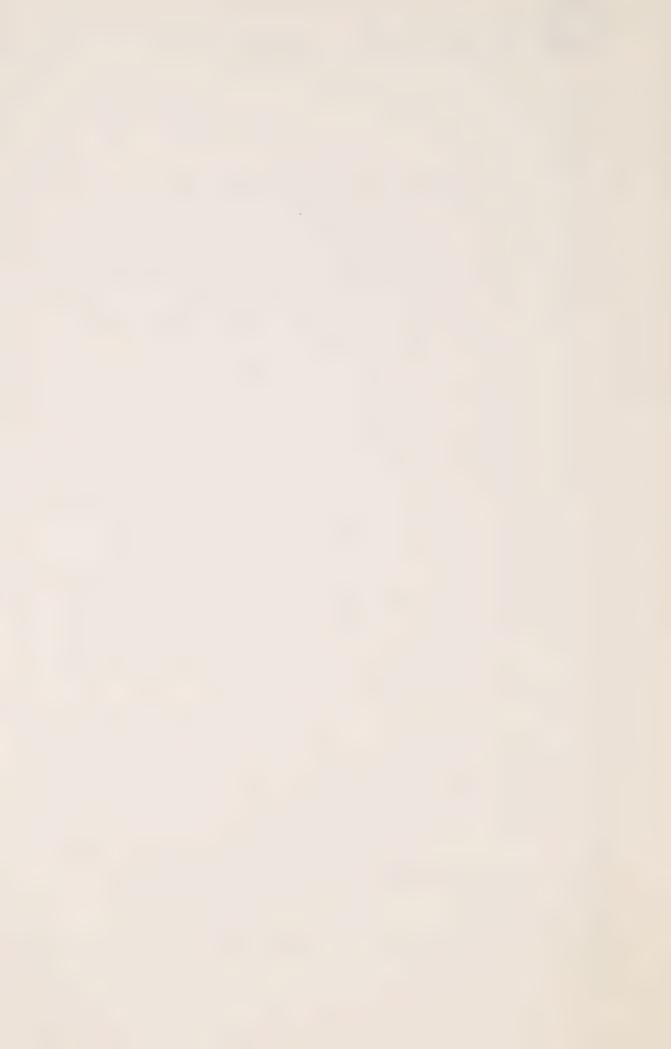
and having regard to the relevant findings at autopsy, in your view is it possible that that degree of damage as affected to the muscle could have resulted in unbinding of digxoin from surrounding tissues so as to account for the post mortem digoxin serum level in this child?

A. Assuming that the ante mortem concentration did not change significantly from the measured level the day before, that was 0.6, I have a difficult time accepting that because we are talking about a 100-fold increase and, to my knowledge, that sort of thing has never been documented or described. It certainly isn't within the realm of reported changes that have taken place post mortem with or without trauma. I suppose again in medicine anything is possible, but it seems to me that it is somewhat unlikely.

Q. Could those resuscitation events, Doctor, and the damage that appears to have been affected to her muscle have caused some degree of elevation in her digoxin levels?

A. I think it could have caused some degree but I can't quite accept 100-fold increase.

Q. Doctor, can we agree as well



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that death in itself is perhaps the most massive tissue insult that one could envisage to an infant.

A. I would think that would be the ultimate, yes.

MR. SCOTT: Do you want to cut down on that?

MS. CRONK: I like that, Mr. Scott.

MR. SCOTT: Can you give it to me

again, please.

MS. CRONK: Death is the most massive tissue insult that one can imagine, and I think he agreed.

Q. Doctor, may we turn then please to the case of Janice Estrella. Your analysis and summary with respect to this child begins at page 7 of your first report to Mr. Wiley. Do you have that, Doctor?

A. Yes.

Q. Doctor, as I understand it, in your original report to Mr.Wiley you concluded that the child's post mortem digoxin levels were excessively high and were compatible with a lethal overdose, even allowing for a post mortem multiplier within known ranges. That was your first conclusion, was it not?



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Α.	That	is	correct.	
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Q. As I understand it, Doctor, the opinion which you expressed in your second reporting letter to Mr. Wiley was materially different.

A. That is correct.

Q. May we turn then, Doctor, please to your second reporting letter?

A. Let me locate that so I have it in frontof me. Okay.

 $\Omega$ . Page 2 of that letter, Doctor, where your discussion with respect to Janice Estrella is set out. The first sentence of your discussion, Doctor, reads:

"My evaluation of the case of Janice
Estrella was based on the erroneous
impression that the post mortem serum
concentrations of digoxin were measured
in venous post mortem blood."

Are we correctly to take it from that, Doctor, that at the time you delivered your first reporting letter to Mr. Wiley the conclusions that you had expressed in that report were premised on the post mortem digoxin level having been achieved in a post mortem blood sample?

A. That was a pivotal piece of



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information in my initial conclusion.

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And if we continue, Doctor, Q. with the first paragraph of your second letter to Mr. Wiley you indicate:

> "However, the post mortem blood samples were obtained from the gutter of the body cavity at the time of autopsy. Data provided by Mr. George Cimbura indicates that while digoxin concentrations in 'gutter blood' may reflect venous blood concentrations in some cases, in others they may vary as much as tenfold from measured concentrations in post mortem blood. This observation confers a high degree of uncertainty on any interpretation of the concentrations measured in gutter blood and requires revision of my initial analysis of the Estrella Case." I take it, Doctor, as the very language

of the report suggests, that once you were informed that the specimen involved was in fact a gutter blood specimen, you were required to substantially alter the opinion you had originally reached.

> Α. That is correct.



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2. Doctor, I am showing to you a copy of what has been marked in these proceedings, Exhibit 238 which, Mr. Commissioner, you may recall is a letter from Mr. Cimbura to Dr. Phillips at the Hospital for Sick Children dated January 31st, 1983 to which is attached a summary of post mortem blood digoxin results.

Can you tell me, Doctor, is that the data concerning gutter blood levels which were provided to you by Mr. Cimbura that you referred to in your report?

- A. Yes, it is.
- Q. Did you as well receive a copy of the covering letter that had been directed to Dr. Phillips?
  - A. Yes, I did.
- Q. Doctor, do you recall when you were provided with this data?
- A. Not specifically, I would have to dig through my files to find out. It was some time after I dictated the report and it probably was sent to me some time in late December or early January before my revision letter.
- Q. All right. Doctor, I would ask you if you would please to turn to page 2 of



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the summary of the post mortem blood digoxin results. The data demonstrates that at least in one case, I suggest to you, Doctor, Case No. 5, that digoxin concentrations measured in the first gutter blood specimen was greatly in excess of that measured in the second from the same patient; that is the level of 169.6 as compared to the subsequent level of 17.7 in the second gutter blood specimen.

- A. That is correct.
- Ω. All right. In the other cases, Doctor, the results on the second gutter blood specimens are, with one or two exceptions, slightly lower than the result measured on the first gutter blood specimen. Would you agree with that?
  - A. That is correct.
- Q. In your report to Mr.Wiley you suggest that the gutter blood results in some cases may vary as much as tenfold from the measured concentrations in post mortem blood. On the basis of this data, Doctor, would you agree that that appears to be the case effectively with respect to Case No. 5 but not with respect to the others?
- A. That's true, that one case is the extreme situation.



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Q. Were you then, Doctor, when you referred to a tenfold elevation, referring to the circumstance demonstrated by Case No. 5 in this study?

A. Yes, that is correct.

learned, that the Estrella level of 72 nanograms on the post mortem specimen was obtained from a gutter blood or pelvic cavity specimen. In light of your knowledge of this case, Doctor, and the results of the gutter blood study which was provided to you, would you, as a pharmacologist, dismiss the 72 nanograms level as meaningless in light of the source and the manner of its sampling?



little else to deal with.



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Α. I wouldn't dismiss it, but I have to have much less confidence in it. The problem this poses is that this was the one piece of information that really made the difference in making that judgment in this case and losing confidence in that number in this particular case really left very

Q. Well, doctor, may we deal first then with what your conclusions were in the face of the knowledge that this was a gutter blood specimen, and I direct you to the last sentence of your reporting letter to Mr. Wiley dealing with Janice Estrella, the second reporting letter. You indicate:

> "Since the measurement of digoxin in the post mortem blood was critical to making a judgment in the Estrella case it is my opinion that this case is open to serious challenge and in itself does not provide a strong basis for a theory of homicide."

Can we in fact, doctor, in your opinion draw any reasonable conclusions regarding digoxin toxicity in this case having regard to the

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yes.

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source and method of sampling of that gutter blood specimen?

I think it is very difficult Α. to draw any conclusions. I think you can't dismiss it, and we have to deal with the 70, and there is a possibility that that really reflects a post mortem concentration. But there is the outside possibility that it could be markedly higher than it actually was post mortem in venous blood. So I think we have to also consider that this may simply have reflected an ante mortem concentration within the therapeutic range. I have difficulty, with any confidence, making a judgment one way or the other.

Ω. Doctor, at the time that you wrote your second reporting letter to Mr. Wiley were you aware that a second post mortem specimen had been taken on Janice Estrella from a leg vein and that it had resulted in a level of greater than 4.7 nanograms?

> Α. I was aware of that sample,

What significance did you 0. attach to that level if any, doctor?

A. Well that was difficult to use because again greater than 4.7 could be anything between 4.8 and 480. You know, it is really -- that is



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about all you can say. It could be totally consistent with a therapeutic ante mortem concentration, or it could be consistent with a post mortem concentration of 70 and it is really not helpful to me beyond that.

- Q. I take it then, doctor --
- A. It really didn't make any difference in my dilemma.
- O. Doctor, as well, apart from the two post mortem specimens, were you at the time of forwarding your second reporting letter to Mr. Wiley aware of the other ante mortem digoxin levels that had been recorded on Janice Estrella?
- A. I believe I was. I would have to look at them specifically but I believe I was aware of them.
  - Q. To help you --
- A. To my knowledge I had access to all of the concentrations that had been measured.
- Q. To help you with that, doctor, the medical record and the digoxin book from the Biochemistry Laboratory at The Hospital for Sick Children indicate that on January 7th, four days prior to this child's death, her level was greater than 5 nanograms. There has been evidence led before the Commissioner to suggest however that on dilution that



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level was in fact greater than 9.4 nanograms; were you aware of that, doctor?

> Yes, I was. Α.

And as well, doctor, on January 8th her level was greater than 4.7, but once again there has been evidence before the Commissioner suggesting that the level was in fact 7.8 nanograms on further dilution; were you aware of that?

- A. I was aware of that.
- Q. And then finally, doctor, on January 9th, two days before the child's death, the level was reported to be greater than 4.7.
  - Α. I think it was 4.7.
- I'm sorry, it is 4.7, you are quite right, doctor. Obviously you were aware of that?
  - Yes, I was aware of that.
- Q. Doctor, were you also aware of the fact that digoxin was ordered held on this child four days prior to her death?
  - Α. That is correct.
- The ante mortem digoxin levels Ω. which had been recorded on this child, doctor, plus the fact that digoxin had been ordered held and that she was not recorded to have received any for four days



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prior to her death, does that assist you in any way apart from the post mortem specimens in assessing whether or not digoxin intoxication had been involved in this child's death?

- Α. Yes, it did.
- 0. In what way, doctor?
- Well, this was the only case in which we have sequential concentrations measured over time without any additional medication being given. So provided with that information I was able to estimate in this patient what the approximate half life would be, excretion of beta phase half life. Then by doing that I was able to estimate at the time of her death approximately what the expected or predicted concentration would have been at the time she died. And making that calculation I came up with a number of somewhat, a little bit greater than 2 nanograms per millilitre which would not be a toxic serum concentration.
- Well, doctor, may we take that 0. in stages please.
  - Yes.
- You said that you were able on the basis of the sequential ante mortem levels to calculate an estimated elimination of half life?





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Α. That is correct.

0. What was your estimate in that

regard?

Α. My estimate was 33 hours.

0. Can you help me, doctor, as to how you get to that number?

Okay. I didn't use the first number from the seven, the first concentration, because I wasn't confident that that was the actual number, it was given to me as greater than 10, 9. something, so I didn't use that because I didn't have confidence in what it actually was. So I used the concentrations from the 8th and 9th I believe of 7. something and 4.7. I assumed that they were taken approximately 24 hours apart, and by doing that I could then, using logarithmic calculations estimate the elimination rate constant and from that calculate the apparent half life.

0. Then after having calculated the apparent half life at 33 hours, doctor, and you have told us that you were then able to calculate what you felt was the likely ante mortem digoxin level at the time of death.

With a rearrangement of the same equation I could plug that elimination rate



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constant back into the equation and ask what would the likely concentration be 24 hours later.

- And your number, doctor, at 0. the end of the calculation for the anticipated ante mortem level at the time of death was what?
  - A . 2.2 nanograms per millilitre.
- And having done that calculation, doctor, in what way did that assist you in making an assessment of this case?

A. I can assume that if no other digoxin had been administered that digoxin toxicity was not a probability and that the patient did not die from digoxin intoxication. That is why the post mortem sample was so pivotal, because if I could document that the predicted ante mortem concentration was a therapeutic concentration and then could have had confidence that that post mortem sample was actually 70, then I would have had a basis for postulating death related to digoxin. In the absence of the confidence in that post mortem level I had to acknowledge that it may not have been due to digoxin intoxication and so I really couldn't say for sure one way or the other.

Doctor, did the results of the 0. toxicology assays done at the Centre for Forensic



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Science help you in this case?

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heart tissues.

- Α. In the tissues?
- 0. Yes.
- Or in the serum? Α.
- 0. In the tissues, in the fixed

Α. They helped me only to the extent that they established that digoxin was present, but that would be expected with a child who had been on long-term digoxin therapy. So they really were not helpful in distinguishing between toxicity and therapeutic digoxin exposure.

Well, doctor, to be clear on 0. that point, in Mr. Cimbura's January 11th report, Exhibit 95A, at page 6, he sets out the results of the concentration assays which were done on the heart tissue specimens; and in this case as you have suggested they were fixed heart tissues, and the reading was 4 nanograms per gram done on both RIA and HPLC/RIA, which Mr. Cimbura has testified in his view led him to believe that he had measured pure digoxin. As well, the Klotz solution in which the tissues had been preserved were assayed.

Did you have regard, doctor, apart from the specific levels that were reported in those



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tissues to the note made by Mr. Cimbura in his report that from the data which he had derived of the tissue specimens he had estimated that the concentration of digoxin in the heart before it was placed in the preservative solution was not less than 55 nanograms per gram; did you have regard to that as well, doctor, for reaching your judgment in this case?

> THE COMMISSIONER: Where do you

find that?

MS. CRONK: I'm sorry, that is the note, sir, on page 6, immediately below the results.

THE COMMISSIONER: Yes. Thank you.

MS. CRONK: On the Estrella sample.

THE WITNESS: This was really not

helpful to me in trying to distinguish between toxicity and therapeutic amounts of digoxin in the body, because this kind of -- if it indeed was in the neighbourhood of 55, would not be unexpected with the therapeutic doses that this child had been on during the months prior to her hospitalization.

Q. If that is true, doctor, then both the estimation of 55 nanograms per gram, and as well the actual digoxin reading in the heart tissue specimen, both are consistent with the therapeutic



GG10 2

doses she had been receiving?

A. They could be, yes. The fixed concentrations simply document for me that it was indeed there, and that is what I would expect in a child who had been on chronic digoxin dosage.

Q. Doctor, without being able to place a high or indeed even a reliable of confidence on the 72 nanograms reading in this case, in your opinion can any opinion be offered as to the likely contribution of digoxin to the death of this child?

A. I can't offer any opinion with any confidence, it would be pure speculation if I gave you an opinion one way or the other.

noment, as you have told us that it is possible, that that 72 nanograms post mortem gutter blood reading did reflect the actual ante mortem concentration; if we assume for the moment that that was the case, as I understand it you did in your original report estimate the amount of a minimum dose which might have been administered to the child to achieve that level, do I have that correctly?

- A. That is correct.
- Q. Doctor, very briefly, could you



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tell us please what the amount of the minimum dose was that you had estimated when you were operating under the assumption that that was a pure sample and a reliable level?

- A. I estimated a dose of approximately .3 mg. could have produced such a concentration in this particular infant.
- $\Omega_{\bullet}$  Doctor, are you referring now to page 7 of your first reporting letter?
- A. I am referring to the third complete paragraph on page 7, approximately half-way down in the paragraph.
- Q. Doctor, continuing from the line of that paragraph where you indicate your estimate for the minimum dose, you further indicate that that amount of a dose, that is 3 mg. -- I am sorry, .3 mg. would require a volume of 3 millilitres of pediatric injectable preparation and 1.2 millilitres of adult injectable preparation, or 6 millilitres of the oral elixir; do I have that correctly?
- A. That is what I had in my initial report, but that is not correct for the pediatric injectable, because I was assuming U.S., a United States product when I said that. The correct volume for the pediatric injectable is 6





elixir?

millilitres, not 3 millilitres.

 $\Omega_{\bullet}$  And is there any change, doctor, when you do the conversion from the U.S. to the Canadian preparation for the adult injectable?

A. No.

 $\Omega$ . And any change to the oral

A. No.





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0. Doctor, then dealing first with the original estimate that you had made for the paediatric injectable preparation, 6 millilitres, can you help us again as to how many vials of the paediatric digoxin we are talking about with that kind of an estimate?

Α. We are talking about six vials.

0. All right. And, Doctor, again with respect to the adult with a volume of 1.2 millilitres, are we talking something less than one adult ampule?

> Α. That is correct.

Q. And with the oral elixir,

Doctor, 6 millilitres?

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Α. It would be a teaspoon.

Q. Did you as well, Doctor, in your original report, again operating under the state of your knowledge at that time, draw any conclusions as to the most likely method of administration?

I had concluded that it was highly unlikely that the dose was administered orally since the infant was extremely ill and was not able to take or retain food by mouth and was



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receiving fluids by nasogastic tube although such a dose could have been put down the nasogastric tube.

It is also somewhat unlikely that the dose was diluted in the IV fluid because as I said before it would take quite a while for it to run in and I was postulating a more rapid infusion.

0. What was your best judgment then at the time as to the likely mode of administration?

I thought that the dose had probably been given intravenously in the intravenous line that was placed on this child and had probably been injected again into the tubing at some point.

And again when you say injected into the tubing, Doctor, are you talking below ---

> Α. Below the volume chamber.

0. Doctor, may we turn then if you would, please, to the case of Kevin Pacsai? Your discussion with respect to this child starts at page 8 of your first reporting letter to Mr. Wiley.

His medical record, Mr. Registrar? Thank you.

Doctor, as I understand it it was your conclusion with respect to Kevin Pacsai as well



that this child received a toxic dose of digoxin which contributed in your view to his death?

- A. That was my conclusion, yes.
- Q. May I ask you, Doctor, as you have done in other cases to please elaborate for us as to the basis upon which you reached this conclusion?

March he had been digitalized at that hospital with a total dose of 48 micrograms per kilogram over 24 hours and subsequently placed on a maintenance dose of digoxin.

He was transferred to the Hospital for Sick Children on 11 March, and at that time he is described as being stable condition with a normal sinus rhythm.

On the evening of the day of his admission he did develop a three to one heart block which means that his upper chambers were beating at a rate three times that of his lower chambers and only every third beat was being conducted to the





lower chamber. But he did revert back to sinus rhythm then and stabilized during the night until approximately 3:45 on 12 March.

At that time he was described as becoming very lethargic, limp; he took his feedings very poorly according to the notes, and again developed a variable heart rate with a two to one block.

He subsequently had a seizure and became apneic on two occasions during this time frame. He did recover from this episode and because of what was going on with him the decision was made apparently to transfer him to the intensive care unit for observation although he had restabilized and as I recall had re-established normal sinus rhythm, normal heart rate, and it was decided to transfer him to the intensive care unit for observation, and that was around 6:00 a.m. I believe on 12 March.

Apparently shortly before his transfer a blood sample was obtained. I have noted 5:30 on 12 March, and that was reported as greater than 10 - my records say it was reported greater than 10 nanograms per mil. but I have no other specific information of whether or not that was ever sorted out as to how much greater.



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This can be compared to a level obtained three days earlier at the referring hospital following his digitalization of 1.8 milligrams per millilitre.

He also was found to have a serum potassium concentration around that time - I have noted 6:30 a.m. - of 9 milli equivalents per litre, and then an hour later, approximately an hour later, 7:20 a.m., .7 milliequivalents per litre.

Following his transfer to the intensive care unit at approximately 8:45 a.m. on 12 March, he sustained a cardiac arrest and they were unable to resuscitate him.

Then measurements of digoxin were made on post mortem blood obtained approximately 24 hours following his death and was found to be in the range of 25 nanograms per millilitre.

The only tissue levels that were available were from fixed tissue in Klotz solution, and as I recall, were consistent either with his recent digitalizing dose - based on those alone I could not differentiate between the digoxin he had received by prescription or a toxic overdose.

His terminal event was consistent with digoxin intoxication although it could have also been



consistent with terminal arrhythmia based on his underlying heart problem.

The thing that concerned me was that this digoxin level obtained at 5:30 a.m. while he was back in sinus rhythm was reported greater than 10 and could have been a toxic concentration to reflect an overdose, particularly when compared to the concentration measured three days earlier.

That in combination with his hyperkalemia, and high potassium and the post mortem concentration all led me to conclude that he sustained high or excessive - had received an excessive dose of digoxin and that his death was related to that.

His inherent dysrhythmia I thought probably made him increasingly susceptible to digoxin so that the concentration of digoxin which might not have been lethally toxic in another-wise normal baby could have produced a fatal arrhythmia in this child because of his underlying heart condition.





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I think it is important to point out that the serum potassium was documented to be normal up until this one drawn at 5:30 a.m. In fact it was 3.9 milliequivalence per litre within 12 hours, approximately 12 hours prior to his death.

There was also absence of any evidence of renal failure in this baby so that we could not blame the hypokalemia or the increased digoxin concentration on kidney failure.

I could not arrive at a specific time of the dose because based on the course, his clinical course from the time of his admission to the time of this death and the concentrations that were measured I thought that that could have occurred from an oral dose given at some time during his hospitalization, excessive amounts of digoxin given orally, or could have been given parenterally, and I could not really based on the information I had distinguish between them and I also had a difficult time placing any kind of a narrow time frame on the time of the dose because of the clinical course and again the kinds of concentrations that were observed.

Q. Thank you, Doctor.

Doctor, there are obviously a number of matters that you have outlined about which I have





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To help you first, though, with respect to the ante mortem serum level which was taken in this case, evidence of Dr. Costigan who is the doctor, the physician who arranged for the taking of that sample, has been that it was taken some time between 6:00 and 6:15 in the morning just after the child was actually transferred to the Intensive Care Unit.

Does that affect your judgment in any way, the differential in timing?

A. Well let me see. Rather than the 5:30 time that I had?

- Q. That is right, Doctor.
- A. The 6 what time again?
- $\Omega$ . Between 6:00 and 6:15 to the best of his recollection, just after the child had been transferred to the Intensive Care Unit.

A. Okay. I don't believe that materially affects my conclusions.

THE COMMISSIONER: You said that the reading was - what did you say?

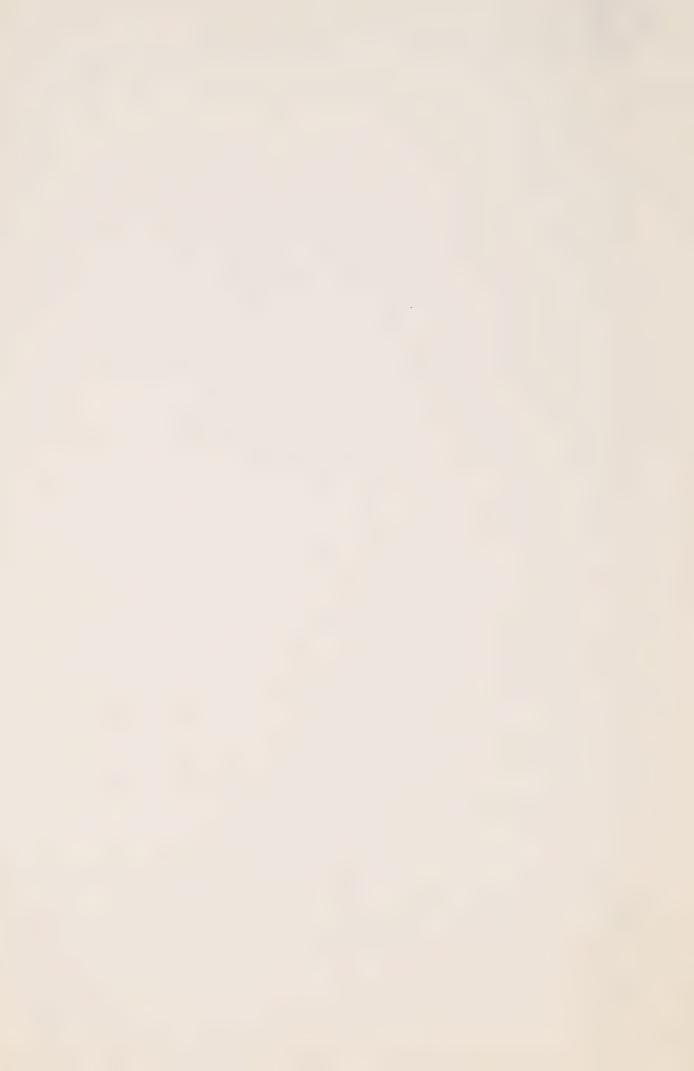
THE WITNESS: The time?

THE COMMISSIONER: No, the reading,

the digoxin level at that time?

THE WITNESS: The level that I had

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3HH3	at that time was reported as greater than 10 nanograms
S	THE COMMISSIONER: That is what I
4	had too, but you also gave it precisely
5	MS. CRONK: No.
6	THE WITNESS: No, I didn't intend
7	to.
8	THE COMMISSIONER: It is getting
	towards the end of the day and I start hearing things
9	MS. CRONK: He did refer, sir, to
10	a level taken three days earlier at the referring
11	hospital which was 1.8.
12	THE COMMISSIONER: I am not confusing
13	it with that. Something clicked in my brain that
14	somebody said it was 12.
15	MS. CRONK: Well, the day is not yet
	over, but I haven't heard that yet.
16	Mr. Commissionr, I note the time.
17	I will be some time on this case, and I am in your
18	hands.
19	THE COMMISSIONER: You don't have
20	to finish this one. Is there some place you would
21	rather stop than right now?
	MS. CRONK: No, sir. Right now
22	would just be fine.
23	THE COMMISSIONER: Because you think





I am losing my senses?

MS. CRONK: No. May I seek counsel,

sir, before I answer that question? Not at all, sir.

THE COMMISSIONER: Well, I don't

know. What do you think? How do you feel about your completion of the examination? Will you be able to do it tomorrow morning?

MS. CRONK: Yes, tomorrow morning,

sir.

THE COMMISSIONER: Then we will

get back at 10 o'clock tomorrow morning.

---Whereupon the hearing adjourned at 4:40 p.m. until Wednesday, November 30th, 1983 at 10:00 a.m.



